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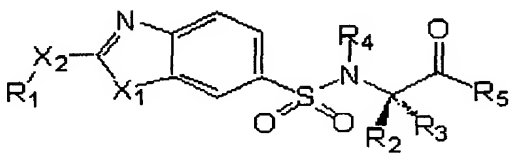
(54) Title: SULFONAMIDE DERIVATIVE AS A MATRIX METALLOPROTEINASE INHIBITOR



(I)

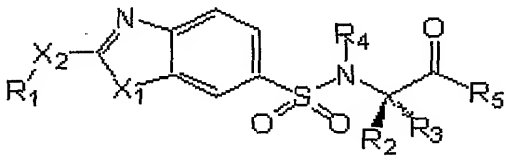
(57) Abstract: The present invention provides a novel sulfonamide derivative of general formula (I) useful as an inhibitor of matrix metalloproteinase (MMP), its isomers, pharmaceutically acceptable salts thereof and a process for preparing the same. Since the sulfonamide derivatives of the present invention selectively inhibit MMP activity *in vitro*, the MMP inhibitors comprising the sulfonamide derivatives as an effective ingredient can be practically applied for the prevention and treatment of all sorts of diseases caused by overexpression and overactivation of MMP.

SULFONAMIDE DERIVATIVE AS A MATRIX METALLOPROTEINASE INHIBITOR

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to sulfonamide derivatives, more specifically, to novel sulfonamide derivatives represented as the following general formula (I), useful as matrix metalloproteinase inhibitor and pharmaceutically acceptable salts thereof and a process for preparing the compounds.



(I)

Description of the Prior Art

Matrix metalloproteinase("MMP") is a Ca^{2+}-dependent proteinase containing zinc ion(Zn^{2+}) at its active site. At least, more than 18 matrix metalloproteinases including stromelycin, collagenase and a family of gelatinase have been identified. MMP degrades various extracellular matrix components of collagen, laminin, proteoglycan, fibronectin, elastin and gelatin under physiological conditions and, therefore, are effective on growth and tissue remodeling of articulation tissue, bone tissue, and connective tissue. The MMP contains Zn^{2+} at its active site and has Ca^{2+}-dependent activity. They are secreted as an inactive form of proenzyme, which is subsequently activated in extracellular side, together with a naturally occuring inhibitor, TIMP(tissue

inhibitor of metalloproteinase)

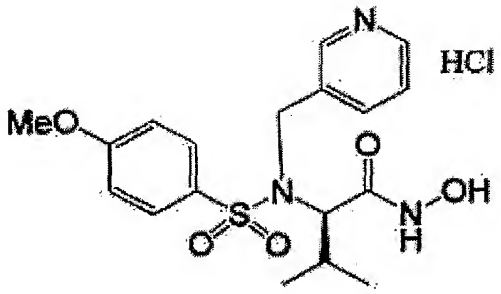
Meanwhile, MMP inhibitor is useful to prevention and treatment of all sorts of diseases caused by overexpression or overactivation of MMP. Such diseases are, for example, rheumatoid, arthrosteitis, unusual bone resorption, osteoporosis, periodontitis, interstitial nephritis, arteriosclerosis, pulmonary emphysema, cirrhosis, cornea injury, metastasis, invasion or growth of tumor cell, autoimmune disease, disease caused by vascular emigration or infiltration of leukocytes, arterialization(see: Beeley et al., Curr. Opin. Ther. Patents, 4(1):7-16, 1994). For instance, it was reported that synthetic MMP inhibitor has an anti-cancer activity *in vivo* along with inhibition of basement membrane remodeling in the mouse model bearing ovarian cancer(see: Cancer Res., 53:2087, 1993). Particularly, considering the fact that MMP-2 and MMP-9 among the above MMP enzymes play an essential role in angiogenesis required for the growth of cancer cells (see: Biochim. Biophys. Acta, 695, 1983), and that MMP-1 and MMP-3 among MMP enzymes play an important role in the progress of arthritis as observed in much higher concentration than normal in the synovium and cartilage of a patient of rheumatoid arthritis(see: Arthritis Rheum., 35:35-42, 1992), the selectivity to MMP-1/MMP-2 is considered to play a crucial role in reducing side effects such as arthralgia. Therefore, researches have been made while focusing on the development of selective inhibitors, and many MMP inhibitors have been designed and synthesized in many aspects(see: J. Enzyme Inhibitor, 2:1-22, 1987; Current Medicinal Chemistry, 2:743-762, 1995; Progress in Medicinal Chemistry, 29:271-334, 1992; Exp. Opin. Ther. Patents, 5:1287-1296, 1995; Drug Discovery Today, 1:16-26, 1996; Chem. Rev., 99:2735-2776, 1999).

Some compounds possessing inhibitory activity against MMP are known. In general, they have a zinc

binding group("ZBG"), which is coordinated to the zinc ion of MMP enzymes at the active site of them. Such ZBGs include hydroxamic acid, carboxylic acid, phosphoric acid, phosphinic acid, thiol and so forth(see: WO 92/09564; WO 95/04033; WO 00/04030; WO 00/43404; WO 95/13289; WO 96/11209; WO 95/09834; WO 95/09620; WO 00/40577; WO 00/40600; WO 98/03166; Chem. Rev. 99:2735-2776, 1999). Especially, several kinds of succinic acid derivatives based on substrate backbone have been designed and synthesized as a peptide-mimic inhibitor. (see: WO 99/25693; WO 98/43959; WO 98/24759; WO 98/30551; WO 98/30541; WO 97/32846; WO 99/01428; EP 897908; WO 98/38179; JP 95002797; WO 99/18074; WO 99/19296; EP 641323). The peptide-mimic inhibitors are known to contain a hydroxamic acid as a ZBG and display a broad spectrum for MMP enzymes.

However, some of the above peptide-mimic inhibitors are often poorly absorbed, exhibiting low oral bioavailability. They are also subject to rapid proteolytic metabolism, thus having short half-life. Furthermore, they possess lower selectivity to MMP-1/MMP-2 and induce the side effect of arthralgia in clinical trial(see: Current Pharmaceutical Design, 5:787-819, 1999; Current Opinion in Drug Discovery & Development, 3:353-361, 2000; Drugs of the Future, 21(12):1215-1220, 1996).

In 1996, non-peptide inhibitors was developed to solve the said problems which are substantially distinguished in terms of chemical structure from the above peptide-mimic inhibitors having simple sulfonyl amino acid derivative represented as a chemical formula below(see: USP 5,506,242; J. Med. Chem., 40:2525-2532, 1997).



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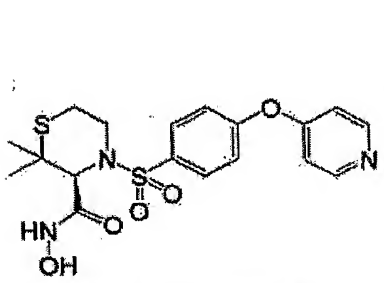
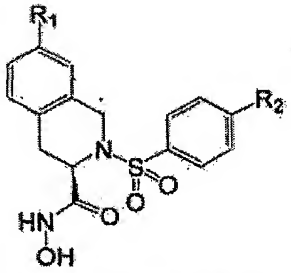
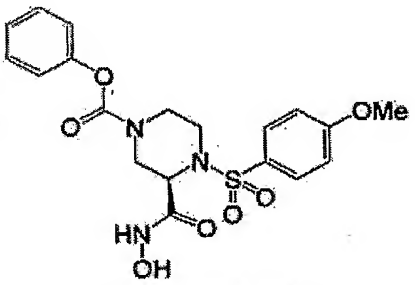
Under a consideration that the small molecule of sulfonamide-derived MMP inhibitors have strong activities *in vitro* against MMP enzymes, and have advantages over the said peptide-mimic inhibitors, a variety of sulfonamide inhibitors have been synthesized and reported in the literature(see: WO 98/50348; WO 97/20824; WO 00/09485; WO 99/58531; WO 99/51572; WO 99/52889; WO 99/52910; WO 99/37625; WO 98/32748; WO 99/18076; WO 99/06410; WO 99/07675; WO 98/27069; WO 97/22587; EP 979816; EP895988; EP 878467; EP 1041072) To improve *in vitro* enzymatic activity, selectivity, and pharmacokinetic profiles, new sulfonamide derivatives have been designed and synthesized, by changing P1′ of the above sulfonamide inhibitor which binds to S1′ sub-site of the enzymes.



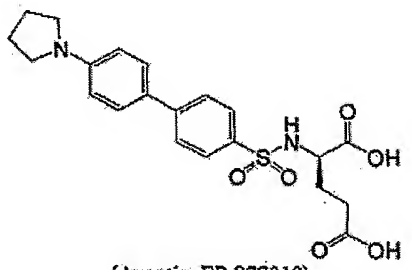
(Agouron, WO 9720824)



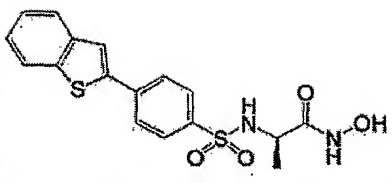
(Aventis, JP 98316662)



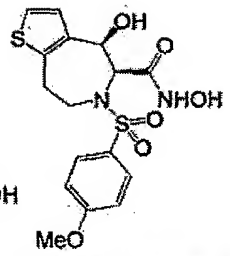
(P&G, WO 9808825)



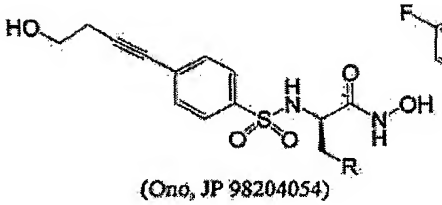
(Aventis, EP 877018)



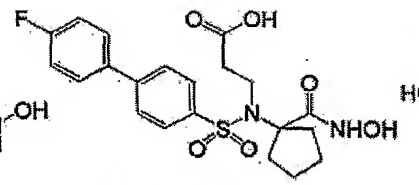
(Ono, JP 98204059)



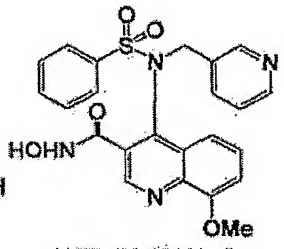
(Amgen, WO 9906410)



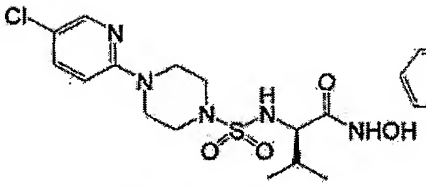
(Ono, JP 98204054)



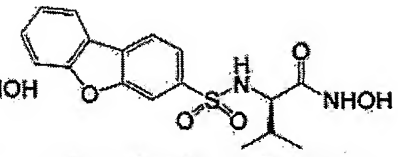
(Pfizer, EP 895988)



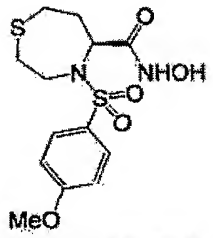
(AHP, EP 9918076)



(Roche, WO 9832748)



(Warner-Lambert, WO 9809934)



(P&G, WO 9808823)

However, while the above sulfonamide inhibitors have relatively high inhibitory activity against MMP, they do not have a higher selectivity to MMP-1/MMP-2 as compared with previous peptide-mimic inhibitors. Some of them have also side effect of arthralgia in clinical trials(see: Current Pharmaceutical Design, 5:787-819, 1999; Current Opinion in Drug Discovery & Development, 3:353-361, 2000; Exp. Opin. Invest. Drugs, 9:2159-2165, 2000; Drugs of the Future, 24(1):16-21, 1999). Although the sulfonamide inhibitors containing a hydroxamic acid as a ZBG typically showed a very strong *in vitro* inhibitory activity as compared with those containing a carboxylic acid as a ZBG, they also have revealed a

limitation in oral administration due to their lower bioavailability and lower metabolic stability *in vivo*(see: J. Med. Chem., 41:640-649, 1988; Investigational New Drugs 16:303-313, 1999; Exp. Opin. Ther. Patents, 10:111-115, 2000; WO 00/63194; WO 00/27808; WO 99/18079; USP 6,117,869).

Under the circumstance, there are strong reasons for developing alternative compounds whose inhibitory action on MMP and the selectivity to MMP-1/MMP-2 are increased to reduce side effects.

SUMMARY OF THE INVENTION

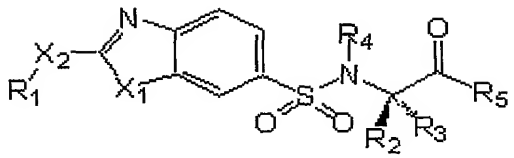
The present inventors have made an effort to develop a new compound in which the inhibitory action on MMP and the selectivity to MMP-1/MMP-2 are increased to reduce side effects, and finally found that a new synthetic inhibitor of sulfonamide derivatives selectively inhibit MMP activity *in vitro*.

A primary object of the present invention is, therefore, to provide a sulfonamide derivative inhibiting MMP activity.

The other object of the invention is to provide a process for preparing the said derivative.

DETAILED DESCRIPTION OF THE INENTION

The present invention provides a sulfonamide derivative, which inhibits MMP activity, represented as the following general formula(I), the isomers and the pharmaceutically acceptable salts thereof, and a process for preparing the above compounds.



(I)

wherein,

R_1 denotes hydrogen, C_{1-12} alkyl, carbocyclic aryl-lower alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-lower alkyl, (oxo, amino or thio) C_{3-7} cycloalkyl, (oxo, amino or thio) C_{3-7} cycloalkyl-lower alkyl, C_{2-12} lower alkenyl, C_{2-12} lower alkynyl, carbocyclic aryl, heterocyclic aryl, heterocyclic aryl-lower alkyl, biaryl, halo lower alkyl, biaryl-lower alkylarylalkyl, hydroxy-lower alkyl, alkoxyalkyl, acyloxy-lower alkyl, alkyl or aryl (thio, sulfinyl or sulfonyl) lower alkyl, (amino, mono or dialkylamino) lower alkyl, acylamino lower alkyl, (N-lower alkyl-piperazino, or N-carbocyclic or heterocyclic aryl-lower alkyl piperazino)-lower alkyl or (morpholino, thiomorpholino, piperidino, pyrrolidino or piperidyl)-lower alkyl;

R_2 denotes hydrogen, lower alkyl, carbocyclic aryl-lower alkyl, C_{1-4} carbocyclic aryl-lower alkyl, C_{1-4} heterocyclic aryl-lower alkyl, C_{1-5} alkoxyphenyl-lower alkyl, C_{1-5} alkenoxyphenyl-lower alkyl, C_{1-5} alkynoxyphenyl-lower alkyl, heterocyclic aryl-lower alkyl, hydroxy-lower alkyl, alkoxyalkyl, acyloxy-lower alkyl, thio-lower alkyl, alkyl or aryl-(thio, sulfinyl or sulfonyl) lower alkyl, (amino, mono or dialkylamino) lower alkyl, carboxyl-lower alkyl, (amino, mono or dialkylamino) lower alkyl or acylamino lower alkyl;

R_3 denotes hydrogen or C_{1-6} lower alkyl;

R_4 denotes hydrogen, C_{1-12} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-lower alkyl, (oxo, amino or thio) C_{3-7} cycloalkyl, (oxo, amino or thio) C_{3-7} cycloalkyl-lower alkyl, carbocyclic aryl, carbocyclic aryl-lower alkyl, heterocyclic aryl, heterocyclic aryl-lower alkyl, biaryl, biaryl-lower alkyl, halo lower

alkyl, hydroxy-lower alkyl, alkoxyalkyl, acyloxy-lower alkyl, alkyl or aryl-(thio, sulfinyl or sulfonyl) lower alkyl, (amino, mono or dialkylamino) lower alkyl, acylamino lower alkyl, carboxyl lower alkyl, (N-lower alkyl-piperazino, or N-carbocyclic or heterocyclic aryl piperazino)-lower alkyl or (morpholino, thiomorpholino, piperidino, pyrrolidino or piperidyl)-lower alkyl;

R_5 denotes hydroxy, alkoxy, halogen, thiol, thioalkoxy or hydroxylamine; and,

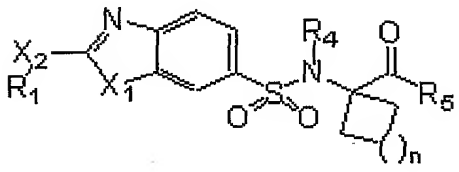
X_1 and X_2 denote N-R_7(wherein, R_7 is hydrogen, C_{1-6} lower alkyl, aryl, heteroaryl or arylalkyl), S or O.

Otherwise mentioned, all kinds of isomers of the above sulfonamide compounds are fallen within the scope of the invention. For instance, in case of alkyl, alkoxy alkene and alkyne, compounds of the invention include isomers due to an asymmetric carbon atom as well as the straight- and branched-chains thereof.

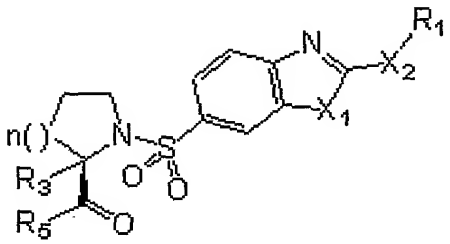
The pharmaceutically acceptable salts of the invention include acid-added salts and hydrates. In general formula(I), the compound of the invention can be converted to the salts corresponding to them, preferably alkali metal salts(sodium, potassium, etc.), alkaline earth metal salts(calcium, magnesium, etc.), ammonium salts, non-toxic salts of pharmaceutical organic amine and water-soluble salts. The compound of the general formula(I) can be converted to inorganic acid salts(hydrochloride, hydrogen bromide, hydrogen iodide, sulfate, phosphate, nitrate, etc.) and organic acid salts(acetate, lactate, tartarate, oxalate, fumarate, glucuronate, etc.), preferably non-toxic salts and water-soluble salts. The compound of the general formula(I) and its salts can be also converted to the hydrates corresponding to them by the conventionally method in the art.

Among the compounds of general formula(I), a cyclic compound may be formed by the linkage of the above

defined R_2 and R_3, which is represented as the general formula(I-1), and a cyclic compound formed by the linkage of R_2 and R_4, which is represented as the general formula(I-2).



(I-1)



(I-2)

wherein,

R_1, R_3, R_4, R_5, X_1 and X_2 are the same as defined in the general formula(I) above; and,

n is an integer of 0 to 4.

Each of the above cyclic compounds can contain hetero-atoms of one or two nitrogens, oxygens, sulfurs, etc.

Two processes for preparing the compounds of the general formula(I) are illustrated by the following steps, which may be applied to the preparation of the compounds, depending physical and chemical properties of R_1.

Process 1: In a case that R_1 does not have an aromatic ring and the carbon which is directly linked with X_2 is a primary carbon

Step 1: Synthesis of intermediate compound(IV)

An amino acid derivative(III) is reacted with a sulfonyl halide(II) in an organic solvent in the

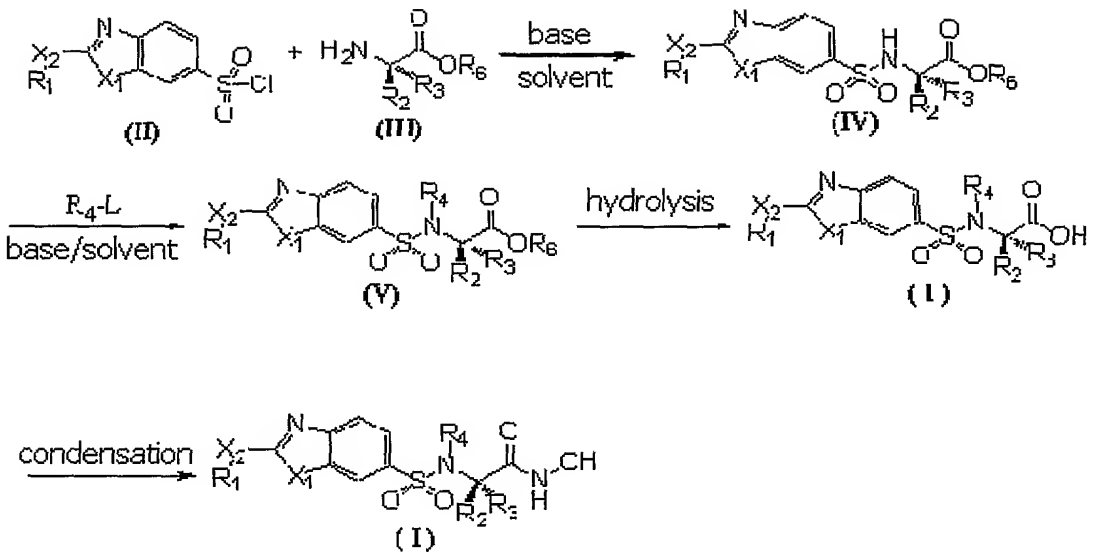
presence of a base to give an intermediate compound(IV): The organic solvent includes most of non-protic solvents, preferably, dichloromethane or dichloroethane, and the base includes triethylamine or N-methylmorpholine.

Step 2: Introduction of R_4 group

The intermediate compound(IV) is reacted with R_4-L (L: reactive leaving group) in an organic solvent in the presence of a base to give an intermediate compound(V): The organic solvent preferably includes DMF, THF or MeCN, and the base includes K_2CO_3, $NaHCO_3$, t-BuOH, NaH, etc.

Step 3: Deprotection of intermediate compound(V)

A protecting group of amino acid, R_6, is removed from the intermediate compound(V) by the hydrolysis in the presence of a base or an acid, or by subjecting in various conditions of H2/Pd-C, KF, etc. to give the compound of the general fomula(I): The base preferably includes NaOH, KOH, LiOH, K_2CO_3, etc. and the acid preferably includes HCl, CF_3CO_2H, etc. In the case that R_6 is silyl group, it is removed by heating the intermediate compound(V) in the presence of F^- of HF, KF, TBAF, etc. or methanol. Optionally, a condensation reaction with hydroxylamine is carried out generally by activating the acid of intermediate compound(V), and reacting with hydroxylamine. The activation of the acid can be made by acid chloride method, mixed anhydride method, active ester method, etc.(see: J. Med. Chem., 40: 2525-2532, 1997; J. Med. Chem., 41:640-649, 1998).

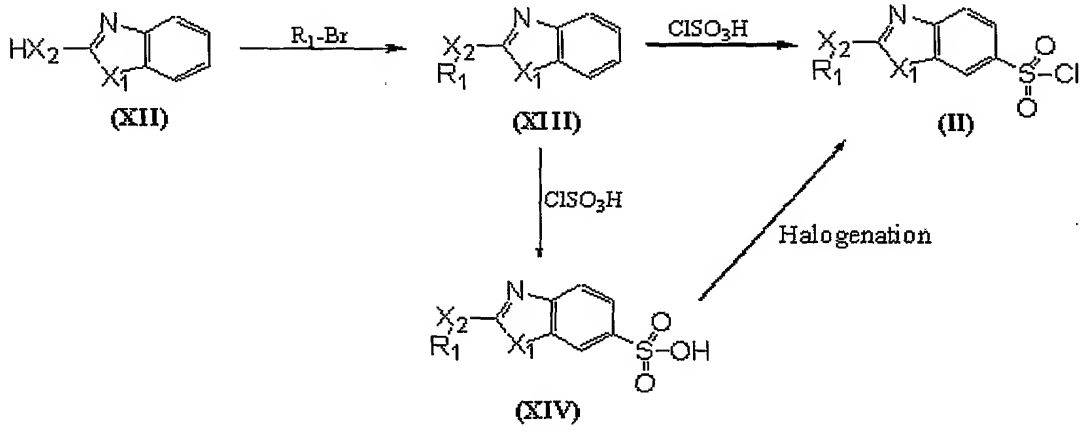


wherein,

R_1, R_2, R_3, R_4, X_1 and X_2 are the same as defined in the general formula(I) above; and,

R_6 is a substituent used as a protecting group of amino acid, such as hydrogen, methyl, ethyl, t-butyl, benzyl, diphenylmethyl or silyl group.

Meanwhile, sulfonyl halide(II) employed as a starting material is prepared as follows:



Step 1: Preparation of compound(XIII)

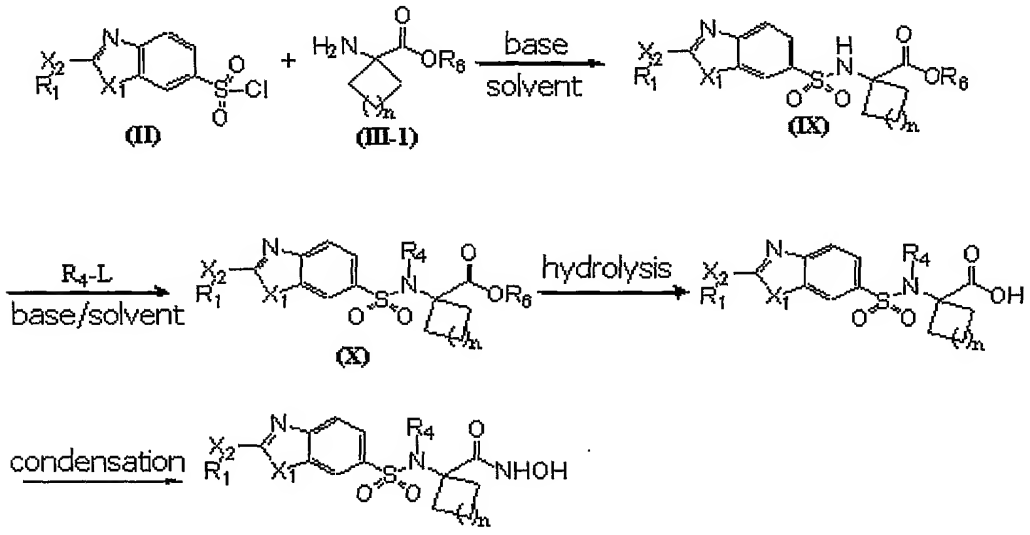
A compound(XII) is subjected to substitution reaction with alkylhalide using an inorganic salt or organic salt at a room temperature to 100°C in an organic solvent to prepare a compound(XIII): The compound(XII) preferably includes 2-mercaptobenzthiazol, 2-mercaptobenzoxazol, hydroxybenzthiazol, hydroxybenzoxazol, halobenzthiazol or halobenzoxazol, and the organic solvent is preferably a mixed solution of water and water-miscible organic solvents.

Step 2: Preparation of sulfonyl halide(II)

Chlorosulfonylation of a compound(XIII) is accomplished by the conventionally known methods below or the partially modified methods(see: USP 4820332, USP 5504098, USP 5985870, USP 5559081, EP 168264, USP 5973148, USP 5962490): For example, chlorosulfonylation of a compound(XIII) is made by reacting the compound (XIII) at a temperature of 50 to 130°C in an organic solvent of dichloromethane, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane, etc., or without organic solvent, in the presence of 2.5 to 5.0 volumes of chlorosulfonic acid. Also, in the reaction, though it is variable depending on the R_1, 2-substituted sulfonic acid(XIV) is obtained as a product along with 2-substituted sulfonylchloride(II) in the form of mixture. Without an isolating step, the mixture is treated with a chlorination reagent of $SOCl_2$, $POCl_3$, PCl_3, etc. to obtain 2-substituted sulfonylchloride(II) only, or the mixture is isolated by recrystallization to give a pure 2-substituted sulfonic acid(XIV) which is then treated with a chlorination reagent of $SOCl_2$, $POCl_3$, PCl_3, etc. to be converted into 2-substituted sulfonylchloride(II).

In the Process 1 above, if the compound(III-1) is employed instead of the amino acid derivative(III), a

cyclic compound formed by the linkage of R_2 and R_3 is prepared as follows, where the compound(III-1) is obtained commercially or prepared by the conventionally known methods(see: WO 9952889; EP 1041072):



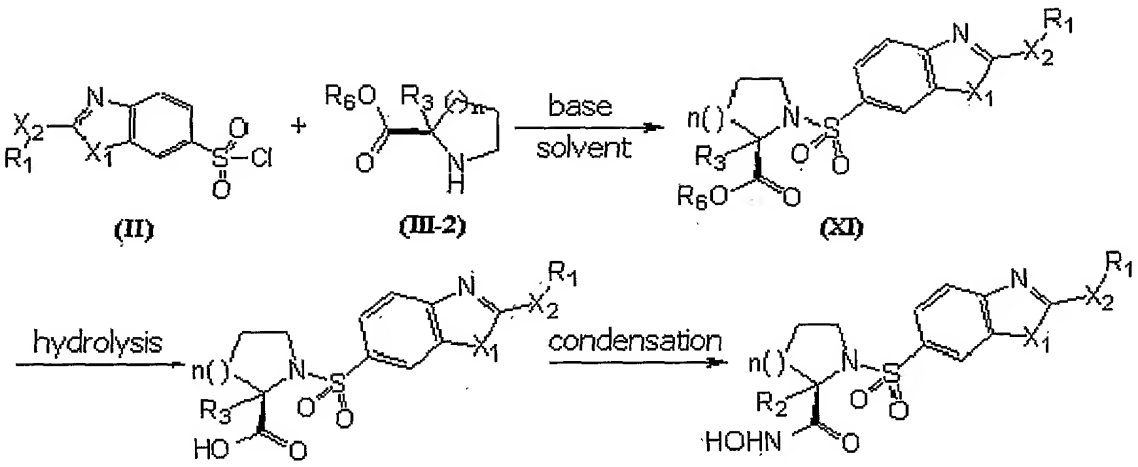
wherein,

R_1, R_4, X_1 and X_2 are the same as defined in the general formula(I) above;

R_6 is a substituent used as a protecting group of amino acid, such as hydrogen, methyl, ethyl, t-butyl, benzyl, diphenylmethyl or silyl group; and,

n is an integer of 0 to 4.

Also, if the compound(III-2) is employed instead of the amino acid derivative(III), a cyclic compound formed by the linkage of R_2 and R_4 is prepared as follows, where the compound(III-2) is obtained commercially or prepared by conventionally known methods(see: USP 5,861,510; USP 5,753,635; WO 97/20824; WO 98/08814; EP 803505; WO 98/08815; WO 98/08825; WO 98/08850; WO 98/50348; EP 878467):



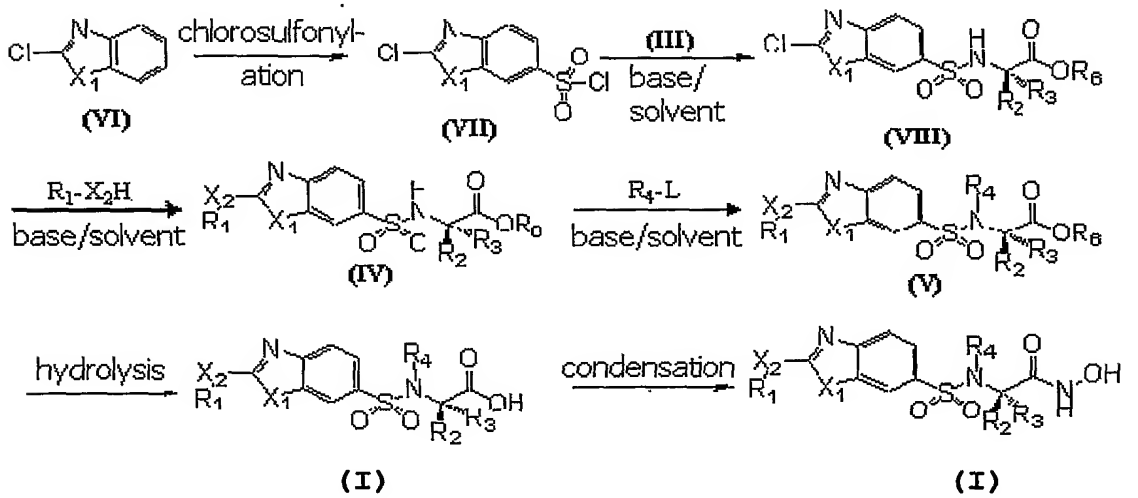
wherein,

R_1, R_3, X_1 and X_2 are the same as defined in the general formula(I) above;

R_6 is a substituent used as a protecting group of amino acid, such as hydrogen, methyl, ethyl, t-butyl, benzyl, diphenylmethyl or silyl group; and,

n is an integer of 0 to 4.

Process 2: In a case that R_1 have an aromatic Ring, or the carbon which is directly linked with X_2 is a secondary carbon or contains a hetero atom



wherein,

R_1, R_2, R_3, R_4, X_1 and X_2 are the same as defined in the general formula(I) above; and,

R_6 is a substituent used as a protecting group of amino acid, such as hydrogen, methyl, ethyl, t-butyl, benzyl, diphenylmethyl or silyl group.

Step 1: Synthesis of sulfonylchloride

The compound(VI) is subjected to the chlorosulfonylation reaction to give a compound(VII).

Step 2: Synthesis of an intermediate compound(VIII)

An amino acid derivative(III) is reacted with the above compound(VII) in an organic solvent in the presence of a base to give an intermediate compound(VIII): The organic solvent includes almost all of non-protic solvents, preferably, dichloromethane or dichloroethane, and the base includes triethylamine or N-methylmorpholine.

Step 3: Substitution of the intermediate compound(VIII) with R_1-X_2H

The intermediate compound(VIII) is reacted with R_1-X_2H at a temperature of 70 to 80°C in an organic solvent in the presence of a base to give an intermediate compound(IV): The organic solvent preferably includes MeCN, THF or DMF, and the base preferably includes K_2CO_3 or $NaHCO_3$.

Step 4: Introduction of R_4

The intermediate compound(IV) is reacted with R_4-L (L:reactive leaving group) in an organic solvent in the presence of a base to give an intermediate compound(V):

The organic solvent preferably includes DMF, THF or MeCN, and the base includes K_2CO_3, $NaHCO_3$, t-BuOH, NaH, etc.

Step 5: Deprotection of intermediate compound(V)

A protecting group of amino acid, R_6, is removed from the intermediate compound(V) by the hydrolysis in the presence of a base or an acid or by subjecting in various conditions of H2/Pd-C, KF, etc. to give the compound of the general fomula(I): The base preferably includes NaOH, KOH, LiOH, K_2CO_3, etc. and the acid preferably includes HCl, CF_3CO_2H, etc. In the case that R_6 is silyl group, it is removed by heating the intermediate compound(V) in the presence of F^- of HF, KF, TBAF, etc. or methanol. Optionally, a condensation reaction with hydroxylamine is carried out generally by activating the acid of intermediate compound(V), and reacting with hydroxylamine. The activation of the acid can be made by acid chloride method, mixed anhydride method, active ester method, etc.(see: J. Med. Chem., 40: 2525-2532, 1997; J. Med. Chem., 41:640-649, 1998).

The present invention is further illustrated in the following examples, which should not be taken to limit the scope of the invention.

Example 1: Preparation of 2-n-butylthio-6-benzthiazolsulfonyl chloride

2-mercaptobenzthiazol(83.4g, 0.5mol) was dispersed in 100 mL of methanol, and added a solution containing 24g of NaOH in 50mL of H_2O. When 2-mercaptobenzthiazol was completely dissolved, n-butylbromide(54mL, 0.5mol) was added and the reaction solution was refluxed for 12 hours. Then, methanol was removed from the solution under reduced pressure and 300mL of ethylacetate was added to the solution which was then washed with H_2O and

1M K_2CO_3 in a sequential order. The separated organic solution was dried over $MgSO_4$ and then distilled under reduced pressure to give about 100g of pure 2-n-butylthio-6-benzthiazol(89%), which was subsequentially transferred to a flask of 500mL without further purification and cooled down to a temperature of 0℃. Chlorosulfonic acid(130g, 2.5 equi.) was slowly added into the flask. The reaction solution was reacted for 24 hours at about 110℃. When starting material was completely exhausted, the reaction solution was cooled down to room temperature(RT) and stirred vigorously after adding ice water. Then, the solid product was obtained by filtering. The filtered solid was treated with ethylacetate(300mL) followed by stirring for 1 hour. The undissolved solid was filtered and washed with ethylacetate to give 2-n-butylthio-6-benzthiazolsulfonic acid(30g). The filtrated ethylacetate solution was treated with 5g of activated carbon and $MgSO_4$ and stirred for 1 hour. Then, the ethylacetate solution was filtered on activated carbon and $MgSO_4$ again and dried under reduced pressure to remove the solvent, to give the titled compound, 2-n-butylthio-6-benzthiazolsulfonyl chloride (about 60g) in a solid form. The titled compound was treated with n-hexane(150mL), followed by stirring for 1 hour. After filtering, pure 2-n-butylthio-6-benzthiazolsulfonyl chloride(55g) was obtained. A 30mL of $SOCl_2$ as solvent and as reagent was added to 2-n-butylthio-6-benzthiazolsulfonic acid(30g) obtained above. The reaction solution was refluxed for 5 hours, dried under reduced pressure, and then, treated with H_2O. The solid product was obtained by filtering. The solid was stirred with ethylacetate(100mL) for 1 hour. The ethylacetate solution was treated with 5g of activated carbon and $MgSO_4$ and stirred for 1 hour. The solution after filtering on activated carbon and $MgSO_4$ was dried under reduced pressure to remove the solvent, to give the titled compound, 2-n-butylthio-6-

benzthiazolsulfonyl chloride(about 30g) in a solid form. The compound was purified with n-hexane as described above, to give a pure 2-n-butylthio-6-benzthiazolsulfonyl chloride(25g). Consquently, about 80g of titled compound(about 56%) was prepared by two processes.

^{1}H NMR(300MHz, $CDCl_3$): δ 1.1(t, 3H), 1.5(m, 2H), 1.8(m, 2H), 3.4(t, 2H), 8.0(dd, 2H), 8.45(s, 1H)

Example 2: Preparation of 2-n-methylthio-6-benzthiazolsulfonyl chloride

The titled compound, 2-n-methylthio-6-benzthiazolsulfonyl chloride was prepared in a similar manner as in Example 1, except for employing iodomethane.

^{1}H NMR(300MHz, $CDCl_3$): δ 2.8(s, 3H), 7.9(dd, 2H), 8.2(s, 1H)

Example 3: Preparation of 2-n-ethylthio-6-benzthiazolsulfonyl chloride

The titled compound, 2-n-ethylthio-6-benzthiazolsulfonyl chloride was prepared in a similar manner as in Example 1, except for employing bromoethane.

^{1}H NMR(300MHz, $CDCl_3$): δ 1.5(t, 3H), 3.4(q, 2H), 7.85(dd, 2H), 8.25(s, 1H)

Example 4: Preparation of 2-n-propylthio-6-benzthiazolsulfonyl chloride

The titled compound, 2-n-propylthio-6-benzthiazolsulfonyl chloride was prepared in a similar manner as in Example 1, except for employing 1-

bromopropane.

^{1}H NMR(300MHz, $CDCl_3$): δ 1.1(t, 3H), 1.9(m, 2H), 3.4(t, 2H), 8.0(dd, 2H), 8.4(s, 1H)

Example 5: Preparation of 2-n-pentylthio-6-benzthiazolsulfonyl chloride

The titled compound, 2-n-pentylthio-6-benzthiazolsulfonyl chloride was prepared in a similar manner as in Example 1, except for employing 1-bromopentane.

^{1}H NMR(300MHz, $CDCl_3$): δ 0.95(t, 3H), 1.4(m, 4H), 1.9(p, 2H), 3.4(t, 2H), 7.9(dd, 2H), 8.3(s, 1H)

Example 6: Preparation of 2-n-hexylthio-6-benzthiazolsulfonyl chloride

The titled compound, 2-n-hexylthio-6-benzthiazolsulfonyl chloride was prepared in a similar manner as in Example 1, except for employing 1-bromohexane.

^{1}H NMR(300MHz, $CDCl_3$): δ 0.9(t, 3H), 1.35(m, 4H), 1.5(m, 2H), 1.85(p, 2H), 3.4(t, 2H), 8.0(dd, 2H), 8.45(s, 1H)

Example 7: Preparation of 2-n-heptylthio-6-benzthiazolsulfonyl chloride

The titled compound, 2-n-heptylthio-6-benzthiazolsulfonyl chloride was prepared in a similar manner as in Example 1, except for employing 1-bromoheptane.

^{1}H NMR(300MHz, $CDCl_3$): δ 0.87(t, 3H), 1.27(m, 6H), 1.5(m, 2H), 1.83(p, 2H), 3.38(t, 2H), 7.85(dd, 2H), 8.24(s, 1H)

Example 8: Preparation of2-n-octylthio-6-benzthiazolsulfonyl chloride

The titled compound, 2-n-octylthio-6-benzthiazolsulfonyl chloride was prepared in a similar manner as in Example 1, except for employing 1-bromooctane.

^{1}H NMR(300MHz, $CDCl_3$): δ 0.82(t, 3H), 1.22(m, 8H), 1.38(m, 2H), 1.73(m, 2H), 3.31(t, 2H), 7.68(dd, 2H), 8.22(s, 1H)

Example 9: Preparation of 2-n-dodecylthio-benzthiazolsulfonyl chloride

The titled compound, 2-n-dodecylthio-6-benzthiazolsulfonyl chloride was prepared in a similar manner as in Example 1, except for employing 1-bromododecane.

^{1}H NMR(300MHz, $CDCl_3$): δ 0.86(t, 3H), 1.27(m, 18), 1.8(m, 2H), 3.4(t, 2H), 8.0(dd, 2H), 8.45(s, 1H)

Example 10: Preparation of 2-cyclohexylmethylthio-6-benzthiazolsulfonyl chloride

The titled compound, 2-cyclohexylmethylthio-6-benzthiazolsulfonyl chloride was prepared in a similar manner as in Example 1, except for employing cyclohexylmethylbromide.

^{1}H NMR(300MHz, $CDCl_3$): δ 1.0(m, 6H), 1.7(m, 3H),

1.9(bd, 2H), 2.1(m, 1H), 3.3(d, 2H),
7.8(dd, 2H), 8.25(s,1H)

Example 11: Preparation of 2-(3-cyclohexyl-1-propylthio)-6-benzthiazolsulfonyl chloride

The titled compound, 2-(3-cyclohexyl-1-propylthio)-6-benzthiazolsulfonyl chloride was prepared in a similar manner as in Example 1, except for employing 3-cyclohexyl-1-propylbromide.

^{1}H NMR(300MHz, $CDCl_3$): δ 0.9(m, 2H), 1.25(m, 4H),
1.37(m, 2H), 1.7(m, 5H), 1.85(m, 2H),
3.35(t, 2H), 7.85(dd, 2H), 8.25(s, 1H)

Example 12: Preparation of 2-n-propylthio-6-benzoxazolsulfonyl chloride

The titled compound, 2-n-propylthio-6-benzoxazolsulfonyl chloride was prepared in a similar manner as in Example 1, except for employing 2-mercaptooxazol instead of 2-mercaptobenzthiazol as starting material and 1-bromopropane as halide.

^{1}H NMR(300MHz, $CDCl_3$): δ 1.1(t, 3H), 1.9(m, 2H),
3,3(t, 3H), 7.8(d, 1H), 8.1(d, 1H),
8.2(s, 1H)

Example 13: Preparation of 2-chloro-6-benzthiazole sulfonyl chloride

2-chloro-6-benzthiazole(1.7g, 10mmol) was cooled down to 0℃ and treated with chlorosulfonic acid(3.3mL) slowly. Then, the reaction solution was subjected at a temperature of 120℃ for 24 hours. When starting material was entirely exhausted, the reaction solution was cooled down to room temperature(RT) and stirred vigorously

after adding ice water. Then, the product was extracted with ethylacetate. The organic phase was washed with H_2O, treated with 5g of activated carbon and $MgSO_4$ and stirred for 1 hour. After removal of activated carbon and $MgSO_4$ by filtration, the filtrated solution was dried under reduced pressure to remove the solvent, to give the titled compound, 2-chloro-6-benzthiazolsulfonyl chloride. The compound was purified on silica gel chromatography by elution with n-hexane, to prepare the titled compound, 2-chloro-6-benzthiazolsulfonyl chloride(1.88g, 70%) in a liquid form.

^{1}H NMR(300MHz, $CDCl_3$): δ 7.9(d, 1H), 8.0(d, 1H), 8.3(s, 1H)

Example 14: Preparation of (2R)-3-methyl-2-[(2-methylthiobenzthiazol-6-sulfonyl)amino] butanoic acid

(D)-valine methylester hydrochloride(0.2g, 1.19mmol) was dispersed in dichloromethane(3mL) and cooled down to 0℃. The reaction solution was treated with triethylamine(0.5mL) and dichloromethane solution in which 2-n-methylthio-6-benzthiazolsulfonyl chloride (0.33g, 1.0equi.) prepared in Example 2 was dissolved in dichloromethane(2mL) while maintaining the temperature of 0℃. When starting material was exhausted after 5 hours, the organic phase was washed with 1N HCl, dried over $MgSO_4$, distilled under reduced pressure and dried under vacuum, to prepare (2R)-3-methyl-2-[(2-methylthiobenzthiazol-6-sulfonyl)amino]butanoic acid methylester(0.35g, 75%).

^{1}H NMR(300MHz, $CDCl_3$): δ 0.88(d, 3H), 0.95(d, 3H), 2.0(m, 1H), 2.8(s, 3H), 3.4(s, 3H), 3.8(m, 1H), 5.2(d, 1H), 7.9(dd, 2H), 8.2(s, 1H)

(2R)-3-methyl-2-[(2-methylthiobenzthiazol-6-sulfonyl)amino]butanoic acid methylester(0.35g, 0.9mmol) was dissolved in THF/H_2O(2mL/2mL), and added LiOH(0.16g, 5equi.). After the reaction soluton was refluxed for 6 hours, the solution was distilled under reduced pressure and treated with 1N HCl. The product was extracted with ethylacetate(10mL). The separated organic phase was washed with NaCl solution, dried over $MgSO_4$, distilled under reduced pressure and dried under vacuum, to prepare the titled compound, (2R)-3-methyl-2-[(2-methylthiobenzthiazol-6-sulfonyl)amino]butanoic acid (54mg, 23%).

^{1}H NMR(300MHz, $CDCl_3$): δ 0.87(d, 3H), 1.0(d, 3H), 2.1(m, 1H), 2.8(s, 1H), 3,72(m, 1H), 5,5(d, 1H), 7.9(m, 2H), 8.3(s, 1H)

Example 15: Preparation of (2R)-N-hydroxy-3-methyl-2-[(2-methylthiobenzthiazol-6-sulfonyl)amino] butyric amide

(2R)-3-methyl-2-[(2-methylthiobenzthiazol-6-sulfonyl)amino]butanoic acid(54mg, 0.15mmol) prepared in Example 14 was dissolved in dichloromethane(2mL) and cooled down to 0℃, and added oxalylchloride(0.04mL, 3equi.) and DMF of catalytic amount. The reaction solution was subjected at room temperature for 3 hours. Then, the reaction solution was distilled and dried under reduced pressure to remove the solvent. And then, (2R)-3-methyl-2-[(2-methylthiobenzthiazol-6-sulfonyl) amino]butanoic chloride thus obtained was dissolved in THF(1mL). Hydroxylamine hydrochloride(0.11g, 10equi.) and $NaHCO_3$(0.15g, 12equi.) were dissolved in THF/H_2O(1mL/1mL) and cooled down to 0℃. The above acid chloride THF solution was slowly added to hydroxylamine solution while maintaining the temperature of 0℃. The

solvent was removed from the reaction solution after 1 hour. Then, the product was extracted with ethylacetate(5mL) and washed with H_2O and 0.1N HCl, dried over $MgSO_4$, distilled under reduced pressure and dried under vacuum, to prepare the titled compound, (2R)-N-hydroxy-3-methyl-2-[(2-methylthiobenzthiazol-6-sulfonyl) amino]butyric amide(50mg, 90%).

^{1}H NMR(300MHz, $CDCl_3$): δ 0.85(d, 6H), 2.0(m, 1H), 2.82(s, 3H), 3.5(m, 1H), 6,6(d, 1H), 7.9(s, 2H), 8.3(s, 1H), 10.5(bs, 1H)

Example 16: Preparation of (2R)-3-methyl-2-[(ethylthio benzthiazol-6-sulfonyl)amino]butanoic acid

Using 2-n-ethylthio-6-benzthiazolsulfonyl chloride prepared above, the titled compound, (2R)-3-methyl-2-[(ethylthiobenzthiazol-6-sulfonyl)amino]butanoic acid was prepared in a similar manner as in Example 14.

^{1}H NMR(300MHz, $CDCl_3$): δ 0.87(d, 3H), 0.95(d, 3H), 1.5(t, 3H), 2.0(m, 1H), 3.4(q, 2H), 3.41(s, 3H), 3.8(m, 1H), 5.2(d, 1H), 7.85(dd, 2H), 8.25(s, 1H)

Example 17: Preparation of (2R)-N-hydroxy-3-methyl-2-[(2-ethylthiobenzthiazol-6 sulfonyl) amino] butyric amide

Using (2R)-3-methyl-2-[(2-ethylthiobenzthiazol-6-sulfonyl)amino]butanoic acid prepared in Example 16, the titled compound was prepared in a similar manner as in Example 15.

^{1}H NMR(300MHz, DMSO-d_6): δ 0.72(m, 6H), 1.4(t, 3H), 1.75(m, 1H), 3.30(q, 2H), 7.77(d, 1H), 7.93(d, 1H), 8.05(d, 1H), 8.4(s, 1H),

8.7(s, 1H), 10.5(s, 1H)

Example 18:

The following titled compounds were prepared by the same process or slightly modified process depending on the properties of starting materials as described in Example 14 or 15.

Example 18-1: (2R)-3-methyl-2-[(2-n-propylthiobenzthiazol-6-sulfonyl)amino]butanoic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.9(d, 3H), 1.0(d, 3H), 1.1(t, 3H), 1.86(m, 2H), 2.1(m, 1H), 3.3(t, 2H), 3.8(m, 1H), 5.3(d, 1H), 7.85(m, 2H), 8.3(s, 1H)

Example 18-2: (2R)-N-hydroxy-3-methyl-2-[(2-n-propylthiobenzthiazol-6-sulfonyl)amino]butyric amide

^{1}H NMR(300MHz, $CDCl_3$): δ 0.8(m, 6H), 1.1(t, 3H), 1.87(m, 2H), 2.0(m, 1H), 3.36(t, 2H), 3.5(m, 1H), 5.5(m, 1H), 7.87(m, 2H), 8.3(s, 1H), 9.5(b, 1H)

Example 18-3: (2R)-3-methyl-2-[(2-n-butylthiobenzthiazol-6-sulfonyl)amino]butanoic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.9(d, 3H), 0.98(d, 3H), 1.0(t, 3H), 1.53(m, 2H), 1.83(m, 2H), 2.1(m, 1H), 3.33(t, 2H), 3.83(m, 1H), 5.3(d, 1H), 7.86(m, 2H), 8.3(s, 1H)

Example 18-4: (2R)-N-hydroxy-3-methyl-2-[(2-n-butylthiobenzthiazol-6-sulfonyl)amino]butyric amide

^{1}H NMR(300MHz, $CDCl_3$): δ 0.8(m, 6H), 1.0(t, 3H),

1.5(m, 2H), 1.8(m, 2H), 2.05(m, 1H),
3.4(t, 2H), 3.6(s, 1H), 5.7(s, 1H),
7.9(d, 2H), 8.3(s, 1H), 9.3(b, 1H)

Example 18-5: (2R)-3-methyl-2-[(2-n-pentylthiobenz-thiazol-6-sulfonyl)amino]butanoic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.9(t, 3H), 0.91(d, 3H),
1.01(d, 3H), 1.43(m, 4H), 1.84(p, 2H),
2.1(m, 1H), 3.3(t, 2H), 3.8(m, 1H),
5.3(d, 1H), 7.8(m, 2H), 8.3(s, 1H)

Example 18-6: (2R)-N-hydroxy-3-methyl-2-[(2-n-pentylthio-benzthiazol-6-sulfonyl)amino]butyric amide

^{1}H NMR(300MHz, DMSO-d_6): δ 0.71(m, 6H), 0.86(t, 3H),
1.36(m, 4H), 1.76(m, 3H), 3.35(q, 2H),
7.8(d, 2H),7.93(d, 1H), 8.0(d, 1H),
8.4(s, 1H), 8.7(s, 1H), 10.4(s, 1H)

Example 18-7: (2R)-3-methyl-2-[(2-n-hexylthiobenz-thiazol-6-sulfonyl)amino]butanoic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.9(m, 6H), 1.0(d, 3H),
1.33(m, 4H), 1.48(m, 2H), 1.83(m, 2H),
2.12(m, 1H), 3.33(t, 2H), 3.83(m, 1H),
5.18(d, 1H), 7.86(q, 2H), 8.28(s, 1H)

Example 18-8: (2R)-N-hydroxy-3-methyl-2-[(2-n-hexyl-thiobenzthiazol-6-sulfonyl)amino]butyric amide

^{1}H NMR(300MHz, DMSO-d_6): δ 0.72(m, 6H), 0.85(t, 3H),
1.3(m, 4H), 1.45(m, 2H), 1.8(m, 3H),
7.7(d, 1H),7.9(d, 1H), 8.1(s, 1H), 8.4(s, 1H),
8.7(s, 1H), 10.5(s, 1H)

Example 18-9: (2R)-3-methyl-2-[(2-n-heptylthio-benzthiazol-6-sulfonyl)amino]butanoic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.9(m, 6H), 1.0(d, 3H), 1.3(m, 6H), 1.5(m, 2H), 1.8(m, 2H), 2.1(m, 1H), 3.32(t, 2H), 3.8(m, 1H), 5.2(d, 1H), 7.9(m, 2H), 8.3(s, 1H)

Example 18-10: (2R)-N-hydroxy-3-methyl-2[(2-n-heptylthio-benzthiazol-6-sulfonyl)amino]butyric amide

^{1}H NMR(300MHz, $CDCl_3$): δ 0.8(m, 9H), 1.27(m, 6H), 1.45(m, 2H), 1.7(m, 2H), 1.9(m, 2H), 3.34(m, 2H), 3.5(m, 1H), 6.5(bd, 1H), 7.3(d, 1H), 7.8(s, 2H), 8.3(s, 1H), 10.4(s, 1H)

Example 18-11: (2R)-3- methyl-2-[(2-n-octylthio benzthiazol-6-sulfonyl)amino]butanoic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.9(m, 6H), 1.0(d, 3H), 1.3(m, 8H), 1.5(m, 2H), 1.8(p, 2H), 2.1(m, 1H), 3.3(t, 2H), 4.75(m, 1H), 5.2(d, 1H), 7.86(m, 2H), 8.28(s, 1H)

Example 18-12: (2R)-N-hydroxy-3-methyl-2-[(2-n-octyl-thiobenzthiazol-6-sulfonyl)amino]butyric amide

^{1}H NMR(300MHz, $CDCl_3$): δ 0.7~0.9(m, 9H), 1.3(m, 8H), 1.5(m, 2H), 1.8(m, 2H), 2.0(m, 1H), 3.4(t, 2H),3.5(m, 1H), 5.5(d, 1H), 7.9(m, 2H), 8.3(s, 1H), 10.1(bs, 1H)

Example 18-13: (2R)-3-methyl-2-[(2-n-dodecylthiobenz-

thiazol-6-sulfonyl)amino]butanoic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.9(m, 6H), 1.0(d, 3H), 1.26(m, 14H), 1.5(m, 2H), 1.8(p, 2H), 2.1(m, 1H), 3.3(t, 2H), 4.8(m, 1H), 5.2(d, 1H),7.85(m, 2H), 8.27(s, 1H)

Example 18-14: (2R)-N-hydroxy-3-methyl-2-[(2-n-dodecyl thiobenzthiazol-6-sulfonyl)amino]butyric amide

^{1}H NMR(300MHz, $CDCl_3$): δ 0.85(m, 9H), 1.26(m, 14H), 1.5(m, 2H),1.8(m, 2H), 2.0(m, 1H), 3.37(t, 2H), 3.6(bs, 1H), 6.4(d, 1H), 7.9(s, 2H), 8.2(s, 1H), 8.4(s, 1H), 10.4(s, 1H)

Example 18-15: (2R)-3-methyl-2-[(2-cyclohexyl-methylthiobenzthiazol-6-sulfonyl)amino] butanoic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.9(d, 3H), 1.0(d, 3H), 1.0~1.3(m, 5H), 1.7(m, 4H), 1.9(m, 2H), 2.1(m, 1H), 3.22(d, 2H), 3.8(m, 1H), 5.4(d, 1H), 7.85(m, 2H), 8.27(s, 1H)

Example 18-16: (2R)-N-hydroxy-3-methyl-2-[(2-cyclohexyl-methylthiobenzthiazol-6-sulfonyl)amino] butyric amide

^{1}H NMR(300MHz, $CDCl_3$): δ 0.85(m, 6H), 1.1(m, 2H), 1.27(m, 3H), 1.78(m, 4H), 1.95(m, 3H), 3.3(d, 2H), 3.6(m, 1H), 6.4(d, 1H), 7.86(s, 2H), 8.3(s, 1H), 10.3(s, 1H)

Example 18-17: (2R)-3-methyl-2-[(2-(1-cyclohexyl-3 propyl) thiobenzthiazol-6-sulfonyl)amino]

butanoic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.9(m, 5H), 1.0(d, 3H), 1.3(m, 4H), 1.5(m, 2H), 1.7(m, 5H), 1.84(m, 2H), 2.2(m, 1H), 3.3(t, 2H), 3.8(m, 1H), 5.2(d, 1H), 7.9(m, 2H), 8.27(s, 1H)

Example 18-18: (2R)-N-hydroxy-3-methyl-2-[(2-(1-cyclohexyl-3-propyl)thiobenzthiazol-6-sulfonyl)amino]butyric amide

^{1}H NMR(300MHz, DMSO-d_6): δ 0.8(m, 6H), 0.9(m, 2H), 1.3(m, 6H), 1.7(m, 5H), 1.85(m, 3H), 3.55(t, 2H), 7.9(d, 1H), 8.0(d, 1H), 8.2(d, 1H), 8.5(s, 1H), 8.8(s, 1H), 10.5(s, 1H)

Example 19: Preparation of (2R)-3-methyl-2-[(2-propylthiobenzoxazol-6-sulfonyl)amino] butanoic acid

(D)-valine methylester hydrochloride (0.2g, 1.19mmol) was dispersed in dichloromethane(3mL) and cooled down to 0℃, and triethylamine(0.37mL, 3equi.) was added. The dichloromethane solution containing 2-n-propylthiobenzoxazol-6-sulfonyl chloride(0.26g, 1.0equi.) prepared in the above Example and dichloromethane(2mL) was also added while maintaining the temperature of 0℃. When starting material was exhausted after 5 hours, the organic phase was washed with 1N HCl, dried over $MgSO_4$, distilled under reduced pressure and dried under vacuum, to give (2R)-3-methyl-2-[(2-propylthiobenzoxazol-6-sulfonyl)amino] butanoic acid methylester(0.31g, 67%).

^{1}H NMR(300MHz, $CDCl_3$): δ 0.86(d, 3H), 0.95(d, 3H),

1.1(t, 3H), 1.87(m, 2H), 2.05(m, 1H),
3.32(t, 2H), 3.43(s, 3H), 3.78(m, 1H),
5.15(d, 1H), 7.64(d, 1H), 7.76(d, 1H),
7.8(s, 1H)

(2R)-3-methyl-2-[(2-propylthiobenzthiazol-6-sulfonyl)amino]butanoic acid methylester(0.19g, 0.48mmol) was dissolved in THF/H_2O(2mL/2mL), and LiOH(0.10g, 5equi.) was added. After reflux for 6 hours, the reaction solution was distilled under reduced pressure and treated with 1N HCl. The product was extracted with ethylacetate(10mL). The separated organic phase was washed with NaCl solution, dried over $MgSO_4$, distilled under reduced pressure and dried under vacuum to prepare the titled compound, (2R)-3-methyl-2-[(2-propylthiobenzoxazol-6-sulfonyl)amino]butanoic acid(0.14g, 77%).

^{1}H NMR(300MHz, $CDCl_3$): δ 0.87(d, 3H), 0.97(d, 3H),
1.22(t, 3H),1.9(m, 2H), 2.1(m, 1H),
3.5(q, 2H), 3.65(m, 1H), 5.7(d, 1H),
7.1(d, 1H), 7.65(m, 2H), 11,7(s, 1H)

Example 20: Preparation of (2R)-N-hydroxy-3-methyl-2-[(2-propylthiobenzoxasol-6-sulfonyl)amino] butyric amide

(2R)-3-methyl-2-[(2-propylthiobenzoxazol-6-sulfonyl)amino]butanoic acid(112mg, 0.3mmol) prepared in Example 19 was dissolved in dichloromethane(2mL) and cooled down to 0℃, and, oxalylchloride(0.08mL, 3equi.) and DMF of catalytic amount were added. After the reaction was completed, the reaction solution was distilled under reduced pressure to remove the solvent and dried under reduced pressure. Then, (2R)-3-methyl-2-[(2-propylthiobenzoxazol-6-sulfonyl)amino]butanoic chloride thus obtained was dissolved in THF(1mL).

Hydroxylamine hydrochloride(0.21g, 10equi.) and $NaHCO_3$(0.303g, 12equi.) was dissolved in THF/H_2O(2mL/2mL) and cooled down to 0℃ to prepare a hydroxylamine solution. Then, acid chloride THF solution was slowly added to the hydroxylamine solution while maintaining the temperature of0℃. After 1 hour, the solvent was removed from the reaction solution. Then, the product was extracted with ethylacetate(5mL), washed with H_2O and 0.1N HCl and dried over $MgSO_4$. The dried material was distilled under reduced pressure and vacuum-dried to prepare the titled compound, (2R)-N-hydroxy-3-methyl-2-[(2-propylthiobenzoxazol-6-sulfonyl)amino]butyric amide (100mg, 85%).

^{1}H NMR(300MHz, DMSO-d_6): δ 0.82(m, 9H), 1.8(m, 2H), 2.1(m, 1H), 3.32(t, 2H), 4.0(m, 1H), 7.25(d, 1H), 7.63(m, 2H), 7.94(d, 1H), 8.76(s, 1H), 10.5(s, 1H)

Example 21: Preparation of (2R)-3-methyl-2-[(2-chlorobenzthiazol-6-sulfonyl)amino]butanoic acid methylester

(D)-valine methylester hydrochloride (0.33g, 2.0mmol) was dispersed in dichloromethane(5mL) and cooled down to 0℃. 2-Chloro-6-benzthiazolsulfonyl chloride(0.5g, 1.0equi.) prepared in Example 13 was dissolved in dichloromethane(3mL) to give a dichloromethane solution. Triethylamine(0.83mL, 3equi.) and the dichloromethane solution were added while maintaining the temperature of 0℃. When starting material was exhausted after 5 hours, the organic phase was washed with 1N HCl, dried over $MgSO_4$ and distilled under reduced pressure. Then, the product was eluted and purified on silica gel chromatography using ethylacetate/n-hexane(1/3) solvent to prepare the titled compound, (2R)-3-methyl-2-[(2-chlorobenzthiazol-6-

sulfonyl)amino] butanoic acid methylester(0.65g, 90%).

^{1}H NMR(300MHz, $CDCl_3$): δ 0.87(d, 3H), 0.96(d, 3H), 2.0(m, 1H), 3.4(s, 3H), 3.8(m, 1H), 5.3(bd, 1H), 7.9(d, 1H), 8.0(d, 1H), 8.33(s, 1H).

Example 22: Preparation of (2R)-3-methyl-2-[(2-phenylthiobenzthiazol-6-sulfonyl)amino] butanoic acid methylester

(2R)-3-methyl-2-[(2-chlorobenzthiazol-6-sulfonyl)amino]butanoic acid methylester(0.154mg, 0.44mmol) prepared in a similar manner as in Example 20 was dissolved in MeCN(3mL) and added solid K_2CO_3(0.1mg, 1.6equi.). Thiophenol(0.055mL, 1.2equi.) was also added and the reaction solution was refluxed for 3 hours. When starting material was disappeared, H_2O/ethylacetate(5mL/10mL) was added for extraction of product. The extracted product in organic phase was washed with NaCl solution, dried over $MgSO_4$ and distilled under reduced pressure. The extracted product was crystallized with n-hexane/ethylacetate(3/1) solution to prepare the titled compound, (2R)-3-methyl-2-[(2-phenylthiobenzthiazol-6-sulfonyl)amino]butanoic acid methylester(190mg, 99%).

^{1}H NMR(300MHz, $CDCl_3$): δ 0.87(d, 3H), 0.95(d, 3H), 2.0(m, 1H), 3.4(s, 3H), 3.76(m, 1H), 5.13(d, 1H), 7.56(m, 3H), 7.8(m, 3H), 8.0(d, 1H), 8.17(s, 1H)

Example 23:

Example 23-1: Preparation of derivative by employing thiophenol derivative as starting material

The following derivatives were prepared in a similar manner as in Example 22, except for employing thiophenol derivative as starting material.

(2R)-3-methyl-2-[(2-(4-methylphenyl)thiobenzthiazol-6-sulfonyl)amino]butanoic acid methylester(400mg, 89%)

(2R)-3-methyl-2-[(2-(4-methoxyphenyl)thiobenzthiazol-6-sulfonyl)amino]butanoic acid methylester(420mg, 89%)

(2R)-3-methyl-2-[(2-(4-bromophenyl)thiobenzthiazol-6-sulfonyl)amino]butanoic acid methylester(430mg, 85%)

(2R)-3-methyl-2-[(2-(4-chlorophenyl)thiobenzthiazol-6-sulfonyl)amino]butanoic acid methylester(424mg, 90%)

(2R)-3-methyl-2-[(2-(4-fluorophenyl)thiobenzthiazol-6-sulfonyl)amino]butanoic acid methylester(430mg, 94%)

(2R)-3-methyl-2-[(2-(4-n-butylphenyl)thiobenzthiazol-6-sulfonyl)amino]butanoic acid methylester(260mg, 80%)

Example 23-2: Preparation of derivative by employing phenol derivative as starting material

The (2R)-3-methyl-2-[(2-phenoxybenzthiazol-6-sulfonyl)amino]butanoic acid methylester was prepared in a similar manner as in Example 22, except for employing phenol derivative as starting material.

^{1}H NMR(300MHz, $CDCl_3$): δ 0.9(d, 3H), 1.0(d, 3H), 2.1(m, 1H), 3.4(s, 3H), 3.8(m, 1H), 5.1(d, 1H), 7.3(m, 1H), 7.4(d, 2H), 7.5(d, 2H), 7.8(m, 2H), 8.2(s, 1H)

Example 23-3: Preparation of derivative by employing benzylthiol derivative as starting material

The following compounds were prepared in a similar manner as in Example 22, except for employing benzylthiol derivative as starting material.

(2R)-3-methyl-2-[(2-(4-methoxyphenyl)methyl-thiobenzthiazol-6-sulfonyl)amino]butanoic acid methyl-ester(1.5g, 75%)

^{1}H NMR(300MHz, $CDCl_3$): δ 0.87(d, 3H), 0.95(d, 3H), 2.04(m, 1H), 3.37(s, 3H), 3.8(s, 3H), 4.6(s, 2H), 5.2(d, 1H), 6.86(d, 2H), 7.37(d, 2H), 7.85(d, 1H), 7.9(d, 1H), 8.2(s, 1H)

(2R)-3-methyl-2-[(2-benzylthiobenzthiazol-6-sulfonyl)amino]butanoic acid methylester (310mg, 75%)

(2R)-3-methyl-2-[(2-(4-chlorophenyl)methyl-thiobenzthiazol-6-sulfonyl)amino]butanoic acid methyl-ester(400mg, 83%)

Example 23-4: Preparation of derivative by employing benzylalkylthiol derivative as starting material

The (2R)-3-methyl-2[(2-(3-phenylethylthio)benz-thiazol-6-sulfonyl)amino]butanoic acid methylester(320mg, 75%) was prepared in a similar manner as in Example 22, except for employing benzalkylthiol derivative as starting material.

Example 23-5: Preparation of derivative by employing aliphatic cyclicthiol derivative as

starting material

The (2R)-3-methyl-2-[(2-cyclopentylthiobenzthiazol-6-sulfonyl)amino]butanoic acid methylester(214mg, 50%) was prepared in a similar manner as in Example 22, except for employing aliphatic cyclicthiol derivative as starting material.

Example 23-6: Preparation of derivative by employing haloalkylthiol derivative as starting material

The (2R)-3-methyl-2-[(2-(3-chloro-1-propylthio)benzthiazol-6-sulfonyl)amino]butanoic acid methylester (240mg, 55%) was prepared in a similar manner as in Example 22, except for employing haloalkylthiol derivative as starting material.

Example 24: Preparation of (2R)-3-methyl-2-[(2-(4-methylphenyl)thiobenzthiazol-6-sulfonyl)amino]butanoic acid and derivative

(2R)-3-methyl-2-[(2-((4-methylphenyl)thiobenzthiazol-6-sulfonyl)amino]butanoic acid methylester(0.3g, 0.66mmol) prepared in Example 23 was dissolved in THF/H_2O(2mL/2mL). LiOH(0.14g, 5equi.) was added and the reaction solution was refluxed for 6 hours. Then, the solution was distilled under reduced pressure and treated with 1N HCl. The organic phase containing product was extracted with ethylacetate(10mL), washed with NaCl solution, dried over $MgSO_4$, distilled and dried under vacuum to prepare the compound, (2R)-3-methyl-2-[(2-(4-methylphenyl)thiobenzthiazol-6-sulfonyl)amino]butanoic acid(0.23 g, 80%).

^{1}H NMR(300MHz, $CDCl_3$): δ 0.85(d, 3H), 0.97(d, 3H), 2.1(m, 1H), 2.5(s, 3H), 3.6(m, 1H),

5.4(d, 1H), 7.34(d, 2H), 7.62(d, 2H),
7.86(m, 2H), 8.16(s, 1H)

The following final materials were prepared under the above hydrolysis condition by employing material prepared in Example 23.

Example 24-1: (2R)-3-methyl-2-[(2-phenylthiobenzthiazol-6-sulfonyl)amino]butanoic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.86(d, 3H), 0.95(d, 3H), 2.0(m, 1H), 3.6(m, 1H), 5.3(d, 1H), 7.56(m, 3H), 7.8(m, 3H), 8.0(d, 1H), 8.17(s, 1H)

Example 24-2: (2R)-3-methyl-2-[(2-(4-methoxyphenyl) thiobenzthiazol-6-sulfonyl)amino]butanoic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.92(d, 3H), 1.0(d, 3H), 2.1(m, 1H), 3.7(m, 1H), 3.9(s, 3H), 5.3(d, 1H), 7.0(d, 2H), 7.6(d, 2H), 7.8(s, 2H), 8.17(s, 1H)

Example 24-3: (2R)-3-methyl-2-[(2-(4-bromophenyl)thio-benzthiazol-6-sulfonyl)amino]butanoic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.8(bm, 6H), 2.1(bm, 1H), 3.7(m, 1H), 7.6(dd, 4H), 7.8(s, 2H), 8.2(s, 1H)

Example 24-4: (2R)-3-methyl-2-[(2-(4-chlorophenyl)thio benzthiazol-6-sulfonyl)amino]butanoic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.8(d, 3H), 0.92(d, 3H), 2.1(m, 1H), 3.6(m, 1H), 5.5(d, 1H),

7.1(d, 2H),7.6(d, 2H), 7.8(m, 2H), 8.2(s, 1H)

Example 24-5: (2R)-3-methyl-2-[(2-(4-fluorophenyl)thio benzthiazol-6-sulfonyl)amino]butanoic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.9(d, 3H), 1.0(d, 3H), 2.1(m, 1H), 3.8(m, 1H), 5.25(d, 1H), 7.24(d, 2H), 7.72(m, 2H), 7.87(m, 2H), 8.20(s, 1H)

Example 24-6: (2R)-3-methyl-2-[(2-((4-n-butylphenyl)thio benzthiazol-6-sulfonyl)amino]butanoic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.9~1.0(m, 9H), 1.4(m, 2H), 1.6(m, 2H), 2.1(m, 2H), 2.7(t, 2H), 3.7(m, 1H), 5.3(d, 1H), 7.34(d, 2H), 7.60(d, 2H), 7.85(m, 2H), 8.18(s, 1H)

Example 24-7: (2R)-3-methyl-2-[(2-phenoxybenzthiazol-6-sulfonyl)amino]butanoic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.9(d, 3H), 1.0(d, 3H), 2.1(m, 1H), 3.8(m, 1H), 5.2(d, 1H), 7.6(m, 3H), 7.75(d, 2H), 7.9(m, 2H), 8.2(s, 1H)

Example 24-8: (2R)-3-methyl-2-[(2-(4-methoxyphenyl) methylthiobenzthiazol-6-sulfonyl)amino] butanoic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.88(d, 3H), 1.0(d, 3H), 2.1(m, 1H), 3.8(s, 3H), 4.53(s, 2H), 5.24(d, 1H), 6.87(d, 2H), 7.35(d, 2H), 7.87(dd, 2H), 8.27(s, 1H)

Example 24-9: (2R)-3-methyl-2-[(2-benzylthiobenzthiazol-6-sulfonyl)amino]butanoic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.88(d, 3H), 1.0(d, 3H), 2.1(m, 1H), 3.8(m, 1H), 4.58(s, 2H), 5.25(d, 1H), 7.33(m, 3H), 7.45(m, 2H), 7.87(dd, 2H), 8.28(s, 1H)

Example 24-10: (2R)-3-methyl-2-[(2-(4-chlorophenyl) methylthiobenzthiazol-6-sulfonyl)amino] butanoic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.88(d, 3H), 1.0(d, 3H), 2.1(m, 1H), 3.8(m, 1H), 4.56(s, 2H), 5.2(d, 1H), 7.3(d, 1H), 7.4(d, 1H), 7.88(dd, 2H), 8.28(s, 1H)

Example 24-11: (2R)-3-methyl-2-[(2-(3-phenylethylthio) benzthiazol-6-sulfonyl)amino]butanoic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.88(d, 3H), 0.98(d, 3H), 2.1(m, 1H), 3.13(t, 2H), 3.56(t, 2H), 3.8(m, 1H), 5.25(d, 1H), 7.28(m, 3H), 7.32(m, 2H), 7.86(m, 2H), 8.27(s, 1H)

Example 24-12: (2R)-3-methyl-2-[(2-cyclopentylthio- benzthiazol-6-sulfonyl)amino]butanoic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.91(d, 3H), 1.0(d, 3H), 1.77(m, 8H), 2.3(m, 1H), 3.8(m, 1H), 4.05(m, 1H), 5.2(d, 1H), 7.86(m, 2H), 8.28(s, 1H)

Example 24-13: (2R)-3-methyl-2-[(2-(3-chloro-propylthio) benzthiazol-6-sulfonyl)amino]butanoic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.89(d, 3H), 1.0(d, 3H),

1.8(m, 2H), 2.3(m, 1H), 3.55(t, 2H),
3.75(t, 2H), 3.9(m, 1H), 5.2(d, 1H),
7.8(m, 2H), 8.28(s, 1H)

Example 25: Preparation of (2R)-N-hydroxy-3-methyl-2-[(2-((4-methylphenyl)thiobenzthiazol-6-sulfonyl)amino]butyric amide and its derivatives

(2R)-3-methyl-2-[(2-((4-methylphenyl)thiobenzthiazol-6-sulfonyl)amino]butanoic acid(84mg, 0.19mmol) prepared in Example 24 was dissolved in dichloromethane(2mL) and cooled down to 0℃. Then, oxalylchloride(0.05mL, 3equi.) and DMF of catalytic amount were added. After reaction for 3 hours at RT, the reaction solution was distilled under reduced pressure to remove the solvent and dried under reduced pressure again to prepare (2R)-3-methyl-2-[(2-((4-methylphenyl)thiobenzthiazol-6-sulfonyl)amino]butanoic chloride. Then, the compound was dissolved in THF(1mL). Hydroxylamine hydrochloride(0.13g, 10equi.) and $NaHCO_3$(0.194g, 12equi.) were dissolved in THF/H_2O(2mL/2mL) and cooled down to 0℃ to give a hydroxylamine solution. Acid chloride THF solution was slowly added to hydroxylamine solution while maintaining the temperature of 0℃. After 1 hour, the solvent was removed from the reaction solution. Then, the product was extracted with ethylacetate(5mL), washed with H_2O and 0.1N HCl, dried over $MgSO_4$, distilled under reduced pressure and vacuum-dried finally to prepare the titled compound, (2R)-N-hydroxy-3-methyl-2-[(2-((4-methylphenyl)thiobenzthiazol-6-sulfonyl)amino]butyric amide(80mg, 92%).

^{1}H NMR(300MHz, DMSO-d_6): δ 0.7(m, 6H), 1.7(m, 1H),
2.4(s, 3H), 3.2(m, 1H), 7.41(d, 2H),
7.7(d, 2H), 7.8(d, 1H), 7.9(d, 1H),

8.0(d, 1H), 8.3(s, 1H), 8.7(s, 1H),
10.5(s, 1H)

The following compounds were prepared under the condition of the above chlorination and hydroxyamine hydrochloride (10equi.) and $NaHCO_3$(12equi.) by employing the acid prepared in Example 24.

Example 25-1: (2R)-N-hydroxy-3-methyl-2-[(2-phenylthio-benzthiazol-6-sulfonyl)amino]butane amide

^{1}H NMR(300MHz, $CDCl_3$): δ 0.83(m, 6H), 2.0(m, 1H), 3.53(m, 1H), 6.4(m, 1H), 7.3(s, 1H), 7.56(m, 3H), 7.76(m, 2H), 7.89(m, 2H), 8.2(s, 1H), 10.3(s, 1H)

Example 25-2: (2R)-N-hydroxy-3-methyl-2-[(2-((4-methoxyphenyl)thiobenzthiazol-6-sulfonyl)amino]butyric amide

^{1}H NMR(300MHz, DMSO-d_6): δ 0.7(m, 6H), 1.7(m, 1H), 3.2(m, 1H), 3.84(s, 3H), 7.15(d, 2H), 7.75(m, 3H), 7.88(d, 1H), 8.0(m, 1H), 8.3(s, 1H), 8.73(s, 1H), 10.5(s, 1H)

Example 25-3: (2R)-N-hydroxy-3-methyl-2-[(2-((4-bromophenyl)thiobenzthiazol-6-sulfonyl)amino]butyric amide

^{1}H NMR(300MHz, DMSO-d_6): δ 0.73(m, 6H), 1.7(m, 1H), 3.24(m, 1H), 7.16(d, 2H), 7.60(d, 2H), 7.84(d, 1H), 7.9(s, 2H), 8.73(s, 1H), 10.4(s, 1H)

Example 25-4: (2R)-N-hydroxy-3-methyl-2-[(2-((4-chlorophenyl)thiobenzthiazol-6-sulfonyl)amino]butyric amide

^{1}H NMR(300MHz, DMSO-d_6): δ 0.73(m, 6H), 1.7(m, 1H), 3.24(m, 1H), 7.18(d, 2H), 7.64(d, 2H), 7.87(d, 1H), 7.95(s, 2H), 8.75(s, 1H), 10.47(s, 1H)

Example 25-5: (2R)-N-hydroxy-3-methyl-2-[(2-((4-fluorophenyl)thiobenzthiazol-6-sulfonyl)amino] butyric amide

^{1}H NMR(300MHz, DMSO-d_6): δ 0.74(m, 6H), 1.7(m, 1H), 3.3(m, 1H), 7.19(d, 2H), 7.65(m, 2H), 7.92(d, 1H), 7.96(s, 2H), 8.76(m, 1H), 10.47(s, 1H)

Example 25-6: (2R)-N-hydroxy-3-methyl-2-[(2-((4-n-butylphenyl)thiobenzthiazol-6-sulfonyl)amino] butyric amide

^{1}H NMR(300MHz, $CDCl_3$): δ 0.8(m, 6H), 0.94(t, 3H), 1.4(m, 2H), 1.6(m, 3H), 2.7(t, 2H), 3.5(bs, 1H), 6.1(bs, 1H), 7.32(d, 2H), 7.63(d, 2H), 7.8(s, 2H), 8.1(s, 1H), 10.1(bs, 1H)

Example 25-7: (2R)-N-hydroxy-3-methyl-2-[(2-phenoxybenzthiazol-6-sulfonyl)amino]butyric amide (120mg, 72%)

Example 25-8: (2R)-N-hydroxy-3-methyl-2-[(2-(4-methoxyphenyl)methylthiobenzthiazol-6-sulfonyl) amino]butyric amide

^{1}H NMR(300MHz, $CDCl_3$): δ 0.85(m, 6H), 1.9(m, 1H), 3.55(m, 1H), 3.78(s, 3H), 4.58(s, 2H), 6.4(d, 1H), 6.87(d, 2H), 7.36(m, 3H), 7.89(m, 2H), 8.29(s, 1H), 10.3(bs, 1H)

Example 25-9: (2R)-N-hydroxy-3-methyl-2-[(2-benzylthio-benzthiazol-6-sulfonyl)amino]butyric amide

^{1}H NMR(300MHz, $CDCl_3$): δ 0.82(m, 6H), 1.22(m, 1H), 3.5(m, 1H), 4.6(s, 2H), 6.2(m, 1H), 7.3(m, 3H), 7.4(m, 2H), 7.86(m, 2H), 8.26(s, 1H), 10.2(s, 1H)

Example 25-10: (2R)-N-hydroxy-3-methyl-2-[(2-(4-chloro-phenyl)methylthiobenzthiazol-6-sulfonyl)amino]butyric amide

^{1}H NMR(300MHz, DMSO-d_6): δ 0.72(m, 6H), 1.7(m, 1H), 3.2(m, 1H), 4.7(s, 2H), 7.38(d, 2H), 7.53(d, 2H), 7.82(d, 1H), 7.95(d, 1H), 7.98(d, 1H), 8.7(s, 1H), 10.5(s, 1H)

Example 25-11: (2R)-N-hydroxy-3-methyl-2-[(2-(3-phenyl-ethylthio)benzthiazol-6-sulfonyl)amino]butyric amide

^{1}H NMR(300MHz, $CDCl_3$): δ 0.75(d, 3H), 0.81(d, 3H), 1.8(m, 1H), 3.13(t, 2H), 3.58(m, 1H), 3.62(t, 3H), 5.8(bs, 1H), 7.28(m, 5H), 7.9(m, 2H), 8.3(s, 1H)

Example 25-12: (2R)N-hydroxy--3-methyl-2-[(2-cyclo-pentylthiobenzthiazol-6-sulfonyl)amino]butyric amide

^{1}H NMR(300MHz, DMSO-d_6): δ 0.72(m, 6H), 1.68(m, 9H), 3.3(m, 1H), 4.1(m, 1H), 7.77(d, 1H), 7.92(d, 1H), 8.0(m, 1H), 8.4(s, 1H), 8.74(s, 1H), 10.5(s, 1H)

Example 26: Preparation of (2R)-3-methyl-2-[(ethylthio-

6-benzthiazolsulfonyl)benzylamino]butanoic acid methylester and other derivatives

(2R)-3-methyl-2-[(2-ethylthiobenzthiazol-6-sulfonyl)amino]butanoic acid methylester(0.16g, 0.376mmol) prepared in a similar manner as in Example 14 was dissolved in DMF(1mL). K_2CO_3(150mg, 3equi.) and benzylbromide(0.056mL, 1.3equi.) were added at RT. After stirring the reaction solution for 1 hour at RT, ethylacetate(5mL) and H_2O were added to afford the phase separation, when starting material was exhausted. The separated organic phase was washed with H_2O for several times, dried over $MgSO_4$ and distilled under reduced pressure to prepare the titled compound, (2R)-3-methyl-2-[(ethylthio-6-benzthiazolsulfonyl)benzylamino]butanoic acid methylester(180mg, 100%).

^{1}H NMR(300MHz, $CDCl_3$): δ 0.82(d, 6H), 1.51(t, 3H), 2.0(m, 1H), 3.36(s, 3H), 3.38(q, 2H), 4.23(d, 1H), 4.6(dd, 2H), 7.21(m, 3H), 7.33(m, 2H), 7.76(d, 1H), 7.83(d, 1H), 8.0(s, 1H)

Example 26-1: (2R)-3-methyl-2-[(methylthio-6-benzthiazolsulfonyl)benzylamino]butanoic acid methylester

^{1}H NMR(300MHz, $CDCl_3$): δ 0.83(d, 6H), 2.0(m, 1H), 2.82(s, 3H), 3.35(s, 3H), 4.23(d, 1H), 4.6(dd, 2H), 7.2(m, 3H), 7.25(m, 2H), 7.8(dd, 2H), 8.0(s, 1H)

Example 26-2: (2R)-3-methyl-2-[(n-propylthio-6-benzthiazolsulfonyl)benzylamino]butanoic acid methylester

^{1}H NMR(300MHz, $CDCl_3$): δ 0.82(d, 6H), 1.1(t, 3H),

1.87(q, 2H), 2.0(m, 1H), 3.36(m, 5H),
4.23(d, 1H), 4.6(dd, 2H), 7.22(m, 3H),
7.33(m, 2H), 7.78(dd, 2H), 8.0(s, 1H)

Example 26-3: (2R)-3-methyl-2-[(n-propylthio-6-benz-oxazolsulfonyl)benzylamino]butanoic acid methylester

^{1}H NMR(300MHz, $CDCl_3$): δ 0.82(m, 6H), 1.1(t, 3H),
1.89(q, 2H), 1.9(m, 1H), 3.32(t, 2H),
3.38(s, 3H), 4.23(d, 1H), 4.6(dd, 2H),
7.22(m, 3H), 7.34(m, 2H), 7.64(dd, 2H),
7.78(s, 1H)

Example 26-4: (2R)-3-methyl-2-[(n-butylthio-6-benz-thiazolsulfonyl)benzylamino]butanoic acid methylester

^{1}H NMR(300MHz, $CDCl_3$): δ 0.82(d, 6H), 0.98(t, 3H),
1.5(m, 2H), 1.82(m, 2H), 2.0(m, 1H),
3.35(s, 3H), 3.38(q, 2H), 4.23(d, 1H),
4.6(dd, 2H), 7.22(m, 3H), 7.33(m, 2H),
7.8(dd, 2H), 8.0(s, 1H)

Example 26-5: (2R)-3-methyl-2-[(n-pentylthio-6-benz-thiazolsulfonyl)benzylamino]butanoic acid methylester

^{1}H NMR(300MHz, $CDCl_3$): δ 0.82(d, 6H), 0.93(t, 3H),
1.45(m, 4H), 1.85(p, 2H), 1.95(m, 1H),
3.35(s, 3H), 3.37(t, 2H), 4.22(d, 1H),
4.65(dd, 2H), 7.22(m, 3H), 7.33(m, 2H),
7.79(dd, 2H), 8.0(s, 1H)

Example 26-6: (2R)-3-methyl-2-[(n-hexylthio-6-benz-thiazolsulfonyl)benzylamino]butanoic acid methylester

^{1}H NMR(300MHz, $CDCl_3$): δ 0.82(d, 6H), 0.9(t, 3H), 1.33(m, 4H), 1.5(m, 2H), 1.8(p, 2H), 2.0(m, 1H), 3.35(s, 3H), 3.37(t, 2H), 4.2(d, 1H), 4.6(dd, 2H), 7.2(m, 3H), 7.3(m, 2H), 7.8(dd, 2H), 8.0(s, 1H)

Example 26-7: (2R)-3-methyl-2-[(n-octylthio-6-benzthiazolsulfonyl)benzylamino]butanoic acid methylester

^{1}H NMR(300MHz, $CDCl_3$): δ 0.82(d, 6H), 0.88(t, 3H), 1.3(m, 8H), 1.5(m, 2H), 1.85(p, 2H), 2.0(m, 1H), 3.35(s, 3H), 3.37(t, 2H), 4.23(d, 1H), 4.6(dd, 2H), 7.22(m, 3H), 7.33(m, 2H), 7.8(dd, 2H), 8.0(s, 1H)

Example 26-8: (2R)-3-methyl-2-[(n-dodecylthio-6-benzthiazolsulfonyl)benzylamino]butanoic acid methylester

^{1}H NMR(300MHz, $CDCl_3$): δ 0.82(d, 6H), 0.85(t, 3H), 1.26(m, 14H), 1.5(m, 2H), 1.8(p, 2H), 2.0(m, 1H), 3.35(s, 3H), 3.37(t, 2H), 4.23(d, 1H), 4.6(dd, 2H), 7.22(m, 3H), 7.33(m, 2H), 7.8(dd, 2H), 8.0(s, 1H)

Example 27: Preparation of (2R)-3-methyl-2-[(ethylthio-6-benzthiazolsulfonyl)benzylamino]butanoic acid and other derivatives

(2R)-3-methyl-2-[(ethylthio-6-benzthiazolsulfonyl) benzylamino]butanoic acid methylester(180mg, 0.376mmol) prepared in Example 26 was dissolved in THF/H_2O(2mL/2mL), and LiOH(0.08g, 5equi.) was added. After reflux for 6 days, the reaction solution was distilled under reduced pressure and treated with 1N HCl, and ethylacetate(10mL)

was added to extract the product. The separated organic phase containing product was washed with NaCl solution, dried over $MgSO_4$ and distilled under reduced pressure. The remaining material was purified on silica gel chromatography using ethylacetate/n-hexane(1/1) and ethylacetate/dichloromethane/acetate(1/1/trace amount) as solvent and dried under vacuum to prepare the titled compound, (2R)-3-methyl-2-[(ethylthio-6-benzthiazolsulfonyl)benzylamino]butanoic acid(0.1g, 57%).

^{1}H NMR(300MHz, $CDCl_3$): δ 0.82(d, 3H), 0.90(d, 3H), 1.5(t, 3H), 2.0(m, 1H), 3.33(q, 2H), 4.24(d, 1H), 4.63(dd, 2H), 7.21(m, 3H), 7.35(m, 2H), 7.79(m, 2H), 8.0(s, 1H)

Example 27-1: (2R)-3-methyl-2-[(hydroxy-6-benzthiazolsulfonyl)benzylamino]butanoic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.83(d, 3H), 0.91(d, 3H), 2.0(m, 1H), 4.1(d, 1H), 4.6(m, 2H), 7.2(m, 3H), 7.3(m, 2H), 7.6(m, 2H), 7.8(s, 1H)

Example 27-2: (2R)-3-methyl-2-[(n-propylthio-6-benzthiazolsulfonyl)benzylamino]butanoic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.8(d, 3H), 0.9(d, 3H), 1.1(t, 3H), 1.8(q, 2H), 2.0(m, 1H), 3.3(t, 2H), 4.25(d, 1H), 4.6(dd, 2H), 7.2(m, 3H), 7.37(m, 2H), 7.75(s, 2H), 8.0(s, 1H)

Example 27-3: (2R)-3-methyl-2-[(n-butylthio-6-benzthiazolsulfonyl)benzylamino]butanoic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.82(d, 3H), 0.9(d, 3H), 0.97(t, 3H), 1.65(m, 2H), 1.8(p, 2H),

2.0(m, 1H), 3.31(t, 2H), 4.23(d, 1H),
4.6(dd, 2H), 7.22(m, 3H), 7.35(m, 2H),
7.78(s, 2H), 8.0(s, 1H)

Example 27-4: (2R)-3-methyl-2-[(n-pentylthio-6-benz-thiazolsulfonyl)benzylamino]butanoic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.82(d, 3H), 0.92(m, 6H), 1.4(m, 4H), 1.8(p, 2H), 2.0(m, 1H), 3.32(t, 2H), 4.23(d, 1H), 4.6(dd, 2H), 7.2(m, 3H), 7.35(m, 2H), 7.8(s, 2H), 8.0(s, 1H)

Example 27-5: (2R)-3-methyl-2-[(n-hexylthio-6-benz-thiazolsulfonyl)benzylamino]butanoic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.82(d, 3H), 0.9(m, 6H), 1.33(m, 4H), 1.45(m, 2H), 1.79(p, 2H), 2.0(m, 1H), 3.3(t, 2H), 4.23(d, 1H), 4.6(dd, 2H), 7.2(m, 3H), 7.35(m, 2H), 7.78(s, 2H), 8.06(s, 1H)

Example 27-6: (2R)-3-methyl-2-[(n-octylthio-6-benz-thiazolsulfonyl)benzylamino]butanoic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.82(d, 3H), 0.9(m, 6H), 1.3(m, 8H), 1.5(m, 2H), 1.8(p, 2H), 2.0(m, 1H), 3.3(t, 2H), 4.23(d, 1H), 4.6(dd, 2H), 7.2(m, 3H), 7.37(m, 2H), 7.78(s, 2H), 8.06(s, 1H)

Example 27-7: (2R)-3-methyl-2-[(n-dodecylthio-6-benz-thiazolsulfonyl)benzylamino]butanoic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.82(d, 3H), 0.87(m, 6H), 1.26(m, 14H), 1.5(m, 2H), 1.8(p, 2H), 2.0(m, 1H), 3.3(t, 2H), 4.2(d, 1H),

4.6(dd, 2H), 7.2(m, 3H), 7.38(m, 2H),
7.8(s, 2H), 8.05(s, 1H)

Example 28: Preparation of (2R)-N-hydroxy-3-methyl-2-[(ethylthio-6-benzthiazolsulfonyl) benzylamino]butyric amide and other derivatives

(2R)-3-methyl-2-[(ethylthio-6-benzthiazolsulfonyl) benzylamino]butanoic acid(50mg, 0.108mmol) prepared in Example 27 was dissolved in dichloromethane(2mL) and cooled down to 0℃. Oxalylchloride(0.094mL, 10equi.) and DMF of catalytic amount were added. Then, the reaction solution was reacted for 3 hours at RT. And then, the solution was distilled and dried under reduced pressure to prepare (2R)-3-methyl-2-[(2-ethylthio-6-benzthiazolsulfonyl)benzylamino]butanoic chloride. The compound was dissolved in in THF(1mL) to give acid chloride THF solution. Hydroxyamine hydrochloride salt(0.08g, 10equi.) and $NaHCO_3$ (0.11g, 12equi.) were dissolved in THF/H_2O(2mL/2mL) and cooled down to 0℃. Acid chloride THF solution was slowly added to hydroxyamine solution while maintaining the temperature of 0℃. After 1 hour, the solvent was removed from the reaction solution. The product was extracted with ethylacetate(5mL), washed with H_2O and 0.1N HCl, dried over $MgSO_4$, distilled under reduced pressure and vacuum-dried to prepare the titled compound, (2R)-N-hydroxy-3-methyl-2-[(ethylthio-6-benzthiazolsulfonyl)benzylamino] butyric amide(52mg, 100%).

^{1}H NMR(300MHz, DMSO-d_6): δ 0.57(d, 3H), 0.84(d, 3H),
1.5(t, 3H), 2.2(m, 1H), 3.36(q, 2H),
3.8(d, 1H), 4.55(dd, 2H), 7.2(m, 3H),
7.3(m, 2H), 7.6(s, 1H), 7.75(s, 1H),
7.9(s, 2H), 9.4(s, 1H)

Example 28-1: (2R)-N-hydroxy-3-methyl-2-[(n-propylthio-6-benzthiazolsulfonyl)benzylamino]butyric amide

^{1}H NMR(300MHz, $CDCl_3$): δ 0.59(d, 3H), 0.82(d, 2H), 1.1(t, 3H), 1.87(m, 2H), 2.2(m, 1H), 3.33(t, 2H), 3.88(d, 2H), 4.61(dd, 2H), 7.18(m, 3H), 7.31(m, 2H), 7.62(d, 1H), 7.7(d, 1H), 7.85(s, 1H), 9.5(s, 1H)

Example 28-2: (2R)-N-hydroxy-3-methyl-2-[(n-butylthio-6-benzthiazolsulfonyl)benzylamino]butyric amide

^{1}H NMR(300MHz, DMSO-d_6): δ 0.72(t, 6H), 0.91(t, 3H), 1.4(m, 2H), 1.7(m, 2H), 1.9(m, 1H), 3.37(t, 2H), 3.8(d, 1H), 4.7(s, 2H), 7.15(m, 3H), 7.35(m, 2H), 7.8(dd, 2H), 8.2(s, 1H), 8.9(s, 1H), 10.7(s, 1H)

Example 28-3: (2R)-N-hydroxy-3-methyl-2-[(n-pentylthio-6-benzthiazolsulfonyl)benzylamino]butyric amide

^{1}H NMR(300MHz, $CDCl_3$): δ 0.75(d, 3H), 0.86(d, 3H), 0.93(t, 3H), 1.43(m, 4H), 1.8(p, 2H), 2.1(m, 1H), 3.36(t, 2H), 3.95(d, 1H), 4.7(s, 2H), 7.15(m, 3H), 7.31(m, 2H), 7.74(dd, 2H), 7.88(s, 1H), 10.5(s, 1H)

Example 28-4: (2R)-N-hydroxy-3-methyl-2-[(n-hexylthio-6-benzthiazolsulfonyl)benzylamino]butyric amide

^{1}H NMR(300MHz, $CDCl_3$): δ 0.49(d, 3H), 0.85(d, 3H), 0.91(t, 3H), 1.35(m, 4H), 1.57(m, 2H), 1.8(p, 2H), 2.2(m, 1H), 3.37(t, 2H),

3.75(d, 1H), 4.58(dd, 2H), 7.24(m, 3H), 7.33(m, 2H), 7.67(d, 1H), 7.83(d, 1H), 7.9(s, 1H), 9.0(s, 1H)

Example 28-5: (2R)-N-hydroxy-3-methyl-2-[(n-octylthio-6-benzthiazolsulfonyl)benzylamino]butyric amide

^{1}H NMR(300MHz, $CDCl_3$): δ 0.54(d, 3H), 0.88(m, 6H), 1.32(m, 8H), 1.5(m, 2H), 1.8(p, 2H), 2.25(m, 1H), 3.36(t, 2H), 3.85(d, 1H), 3.6(dd, 1H), 7.2(m, 3H), 7.31(m, 2H), 7.65(d, 1H), 7.85(d, 1H), 7.92(s, 1H), 9.2(s, 1H)

Example 28-6: (2R)-N-hydroxy-3-methyl-2-[(n-dodecylthio-6-benzthiazolsulfonyl)benzylamino]butyric amide

^{1}H NMR(300MHz, $CDCl_3$): δ 0.52(d, 3H), 0.85(m, 6H), 1.26(m, 16H), 1.5(m, 2H), 1.8(p, 2H), .25(m, 1H), 3.35(t, 2H), 3.8(d, 1H), 4.6(dd, 2H), 7.22(m, 3H), 7.31(m, 2H), 7.65(d, 1H), 7.85(d, 1H), 7.9(s, 1H), 9.2(s, 1H)

Example 29: Preparation of (2R)-2-[(2-n-pentyl-thiobenzthiazol-6-sulfonyl)amino]propionic acid and other derivatives

(D)-alaninemethylester hydrochloride(0.2g, 1.43 mmol) was dispersed in dichloromethane(3 mL) and cooled down to 0℃. 2-n-pentylthio-6-benzthiazolsulfonyl chloride(0.39g, 1.0equi.) prepared in the above Example was dissolved in dichloromethane(2mL). Triethylamine(0.6mL, 3equi.) and the dichloromethane solution prepared above were added while maintaining the

temperature of 0℃. When starting material was disappeared after 5 hours, the organic phase was washed with 1N HCl solution, dried over $MgSO_4$, distilled under reduced pressure and vacuum-dried to prepare the titled compound, (2R)-2-[(2-n-pentylthiobenzthiazol-6-sulfonyl) amino]propionic acid methylester(0.4g, 69%).

^{1}H NMR(300MHz, $CDCl_3$): δ 0.94(t, 3H), 1.41(d, 3H), 1.42(m, 4H), 1.86(p, 2H), 3.39(t, 2H), 3.52(s, 3H), 4.05(p, 1H), 5.31(d, 1H), 7.91(dd, 2H), 8.28(s, 1H)

(2R)-2-[(2-n-pentylthiobenzthiazol-6-sulfonyl) amino]propionic acid methylester(0.22g, 0.547mmol) was dissolved in THF/H_2O(2mL/2mL) and treated with LiOH(0.115g, 5equi.). After reflux for 6 hours, the reaction solution was distilled under reduced pressure to remove the solvent and treated with 1N HCl solution, and ethylacetate(10mL) was added to extract product. Then, the separated organic phase was washed with NaCl solution, dried over $MgSO_4$, distilled under reduced pressure and vacuum-dried to prepare the titled compound, (2R)-2-[(2-n-pentylthiobenzthiazol-6-sulfonyl)amino] propionic acid(0.2mg, 94%).

^{1}H NMR(300MHz, $CDCl_3$): δ 0.92(t, 3H), 1.45(m, 7H), 1.83(p, 2H), 3.35(t, 3H), 4.04(p, 1H), 5.45(d, 1H), 7.86(m, 2H), 8.28(s, 1H)

The following titled compounds were prepared by employing other sulfonyl chloride instead of 2-n-pentylthio-6-benzthiazolsulfonyl chloride used in the above process.

Example 29-1: (2R)-2-[(2-n-hexylthiobenzthiazol-6-sulfonyl)amino]propionic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.90(t, 3H), 1.34(m, 4H), 1.45(m, 5H), 1.83(p, 2H), 3.32(m, 2H), 4.05(p, 1H), 5.4(d, 1H), 7.86(m, 2H), 8.29(s, 1H)

Example 29-2: (2R)-2-[(2-(cyclohexylmethylthio) benzthiazol-6-sulfonyl)amino]propionic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 1.10(m, 2H), 1.24(m, 3H), 1.45(d, 3H), 1.80(m, 4H), 1.95(d, 2H), 3.26(d, 2H), 4.06(m, 1H), 5.45(d, 1H), 7.88(m, 2H), 8.30(s, 1H)

Example 30:

The following titled compounds were prepared in a similar manner as in Example 29, except for employing such amino acids as (D)-phenylalanine, (D)-methionine, (D)-leucine, (D)-aspartic acid, (D)-glutamic acid, (D)-tryptophan methylester and (±)-2-amino-2-methyl-3-phenylpropionic acid ethylester.

Example 30-1: (2R)-2-[(2-n-pentylthiobenzthiazol-6-sulfonyl)amino]-3-phenylpropionic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.93(t, 3H), 1.40(m, 4H), 1.83(p, 2H), 3.12(dd, 1H), 3.12(dd, 1H), 3.33(t, 2H), 4.2(m, 1H), 5.2(d, 1H), 7.08(m, 2H), 7.18(m, 3H), 7.75(dd, 2H), 8.07(s, 1H)

Example 30-2: (2R)-2-[(2-n-hexylthiobenzthiazol-6-sulfonyl)amino]-3-phenylpropionic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.90(t, 3H), 1.33(m, 4H), 1.55(m, 2H), 1.82(p, 2H), 2.99(dd, 1H),

3.15(dd, 1H), 3.34(t, 2H), 4.25(m, 1H),
5.2(d, 1H), 7.09(m, 2H), 7.2(m, 3H),
7.71(d, 1H), 7.79(d, 1H), 8.07(s, 1H)

Example 30-3: (2R)-2-[(2-(cyclohexylmethylthio)benzthiazol-6-sulfonyl)amino]-3-phenylpropionic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 1.09(m, 2H), 1.25(m, 3H),
1.71(m, 4H), 1.93(d, 2H), 3.0(dd, 1H),
3.11(dd, 1H), 3.27(d, 2H), 4.15(m, 1H),
5.6(d, 1H), 7.15(m, 5H), 7.74(dd, 2H),
8.08(s, 1H)

Example 30-4: (2R)-4-methylthio-2-[(2-n-pentylthio-benzthiazol-6-sulfonyl)amino]butyric acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.93(t, 3H), 1.40(m, 4H),
1.83(m, 2H), 1.9(m, 1H), 2.06(s, 3H),
2.1(m, 1H), 2.57(m, 2H), 3.32(t, 2H),
4.2(m, 1H), 5.5(d, 1H), 7.87(m, 2H),
8.30(s, 1H)

Example 30-5: (2R)-4-methylthio-2-[(2-n-hexylthiobenz-thiazol-6-sulfonyl)amino]butyric acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.92(t, 3H), 1.33(m, 4H),
1.5(m, 2H), 1.83(m, 2H), 1.9(m, 1H),
2.06(s, 3H), 2.1(m, 1H), 2.55(m, 2H),
3.32(t, 2H), 4.15(m, 1H), 5.47(d, 1H),
7.88(m, 2H), 8.30(s, 1H)

Example 30-6: (2R)-4-methylthio-2-[(2-(cyclohexyl-methylthio)benzthiazol-6-sulfonyl)amino]butyric acid

^{1}H NMR(300MHz, $CDCl_3$): δ 1.15(m, 2H), 1.24(m, 3H),

1.74(m, 4H), 1.90(m, 3H), 2.06(s, 1H),
2.1(m, 1H), 2.57(m, 2H), 3.22(d, 2H),
4.2(m, 1H), 5.54(d, 1H), 7.87(m, 2H),
8.3(s, 1H)

Example 30-7: (2R)-4-methyl-2-[(2-n-pentylthiobenz-thiazol-6-sulfonyl)amino]valeric acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.93(m, 9H), 1.4(m, 4H),
1.5(m, 2H), 1.83(p, 3H), 3.33(t, 2H),
4.0(m, 1H), 5.18(d, 1H), 7.87(m, 2H),
8.28(s, 1H)

Example 30-8: (2R)-4-methyl-2-[(2-n-hexylthio-benzthiazol-6-sulfonyl)amino]valeric acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.91(m, 9H), 1.34(m, 4H),
1.54(m, 4H), 1.84(m, 3H), 3.33(t, 2H),
4.0(m, 1H), 5.1(m, 1H), 7.86(m, 2H),
8.28(s, 1H)

Example 30-9: (2R)-2-[(2-pentylthiobenzthiazol-6-sulfonyl)amino]succinic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 1.90(t, 3H), 1.26(m, 2H),
1.45(m, 2H), 1.79(p, 2H), 2.9(dd, 1H),
3.1(dd, 1H), 3.37(t, 2H), 4.15(m, 1H),
6.1(d, 1H), 7.9(s, 2H), 8.3(s, 1H)

Example 30-10: (2R)-2-[(2-hexylthiobenzthiazol-6-sulfonyl)amino]succinic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.9(t, 3H), 1.3(m, 4H),
1.5(m, 2H), 1.75(p, 2H), 2.9(dd, 1H),
3.1(dd, 1H), 3.3(t, 2H), 4.2(m, 1H),
6.7(d, 1H), 7.83(s, 2H), 8.23(s, 1H)

Example 30-11: (2R)-2-[(2-pentylthiobenzthiazol-6-sulfonyl)amino]glutaric acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.93(t, 3H), 1.41(m, 4H), 1.84(m, 3H), 2.15(m, 1H), 2.45(m, 2H), 3.36(t, 2H), 3.95(m, 1H), 5.9(d, 1H), 7.87(s, 1H), 8.28(s, 1H)

Example 30-12: (2R)-2-[(2-hexylthiobenzthiazol-6-sulfonyl)amino]glutaric acid

^{1}H NMR(300MHz, DMSO-d_6): δ 0.86(t, 3H), 1.30(m, 4H), 1.45(m, 2H), 1.75(m, 2H), 1.9(m, 1H), 2.1(m, 1H), 2.4(m, 2H), 3.32(t, 2H), 3.85(m, 1H), 5.8(m, 1H), 7.83(s, 2H), 8.24(s, 1H)

Example 30-13: (2R)-2-[(2-pentylthiobenzthiazol-6-sulfonyl)amino]-3-(1H-indole-3-yl) propionic acid

^{1}H NMR(300MHz, DMSO-d_6): δ 0.86(t, 3H), 1.36(m, 4H), 1.76(m, 2H), 2.8(dd, 1H), 3.1(dd, 1H), 3.37(t, 2H), 3.87(m, 1H), 6.78(t, 1H), 6.90(t, 1H), 7.04(s, 1H), 7.14(m, 2H), 7.53(d, 1H), 7.69(d, 1H), 8.13(s, 1H), 8.3(d, 1H), 10.74(s, 1H)

Example 30-14: (±)-2-[(2-n-hexylthiobenzthiazol-6-sulfonyl)amino]-2-methyl-3-phenylpropionic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.9(t, 3H), 1.34(m, 4H), 1.48(m, 5H), 1.8(p, 2H), 3.1(d, 1H), 3.3(d, 1H), 3.35(t, 1H), 5.45(s, 1H), 7.27(m, 5H), 7.85(s, 2H), 8.0(s, 1H), 8.2(s, 1H)

Example 31: Preparation of (2R)-N-hydroxy-2-[(2-n-pentylthiobenzthiazol-6-sulfonyl)amino] propionamide

(2R)-2-[(2-n-pentylthiobenzthiazol-6-sulfonyl) amino]propionic acid(190mg, 0.49mmol) prepared in Example 29 was dissolved in dichloromethane(2mL) and cooled down to 0℃. Oxalylchloride(0.17mL, 4equi.) and DMF of catalytic amount were added and the reaction solution was refluxed for 3 hours at RT. Then, the solution was distilled under reduced pressure to remove the solvent and dried under reduced pressure to give (2R)-2-[(2-n-pentylthiobenzthiazol-6-sulfonyl)amino] propionic chloride. And then, the compound was dissolved in THF(2mL) to obtain acid chloride THF solution. Hydroxyamine hydrochloride salt(0.34g, 10equi.) and $NaHCO_3$(0.49g, 12equi.) was dissolved in THF/H_2O(1mL/1mL) and cooled down to 0℃. Acid chloride THF solution was slowly added to hydroxyamine solution at 0℃, and the solvent was removed after 1 hour. Then, the product was extracted with ethylacetate(5mL), washed with H_2O and 0.1N HCl, dried over $MgSO_4$, distilled and vacuum-dried to prepare the titled compound, (2R)-N-hydroxy-2-[(2-n-pentylthiobenzthiazol-6-sulfonyl)amino] propion amide (190 mg, 97%).

^1H NMR(300MHz, $CDCl_3$): δ 0.93(s, 3H), 1.23(m, 3H), 1.43(m, 4H), 1.86(p, 2H), 3.37(t, 2H), 3.85(m, 1H), 6.6(m, 1H), 7.88(s, 1H), 8.29(s, 1H), 10.2(s, 1H)

Example 32: Preparation of various hydroxamic acids

The following hydroxamic acids were produced in a similar manner as in Example 31 by employing various acid derivatives prepared in Examples 29 and 30.

Example 32-1: (2R)-N-hydroxy-2-[(2-n-hexylthio benzthiazol-6-sulfonyl)amino]propionamide

^{1}H NMR(300MHz, $CDCl_3$): δ 0.89(t, 3H), 1.23(m, 3H), 1.33(m, 4H), 1.49(m, 2H), 1.85(m, 2H), 3.37(t, 2H), 4.9(m, 1H), 6.55(d, 1H), 7.88(m, 2H), 8.3(s, 1H), 10.2(s, 1H)

Example 32-2: (2R)-N-hydroxy-2-[(2-(cyclohexyl-methylthio)benzthiazol-6-sulfonyl)amino] propionamide

^{1}H NMR(300MHz, $CDCl_3$): δ 1.06~1.28(m, 8H), 1.76(m, 4H), 2.0(m, 2H), 3.24(d, 2H), 3.9(m, 1H), 6.2(s, 1H), 7.87(s, 2H), 8.3(s, 1H)

Example 32-3: (2R)-N-hydroxy-2-[(2-n-pentylthiobenz-thiazol-6-sulfonyl)amino]-3-phenylpropion amide

^{1}H NMR(300MHz, $CDCl_3$): δ 0.93(t, 3H), 1.5(m, 4H), 1.8(p, 2H), 2.8(dd, 1H), 3.05(dd, 1H), 3.37(t. 2H), 4.0(m, 1H), 6.3(m, 1H), 7.0(m 5H), 7.6(d, 1H), 7.7(d, 1H), 7.93(s, 1H), 10.1(s, 1H)

Example 32-4: (2R)-N-hydroxy-2-[(2-n-hexylthio-benzthiazol-6-sulfonyl)amino]-3-phenylpropionamide

^{1}H NMR(300MHz, $CDCl_3$): δ 0.88(t, 3H), 1.33(m, 4H), 1.47(m, 2H), 1.81(m, 2H), 2.8(m, 1H), 3.0(m, 1H), 3.34(t, 2H), 4.0(m, 1H), 6.5(m, 1H), 6.98(s, 5H), 7.66(dd, 2H), 7.89(s, 1H), 10.2(s, 1H)

Example 32-5: (2R)-N-hydroxy-2-[(2-(cyclohexyl-methylthio)benzthiazol-6-sulfonyl)amino]-3-phenylpropionamide

^{1}H NMR(300MHz, $CDCl_3$): δ 1.2(m, 5H), 1.7(m, 4H), 1.93(m, 2H), 2.85(m, 1H), 3.1(m, 1H), 3.3(d, 2H), 3.95(m, 1H), 5.55(s, 1H), 6.86(m, 2H), 7.0(m, 3H), 7.55(d, 1H), 7.75(d, 1H), 7.9(s, 1H)

Example 32-6: (2R)-N-hydroxy-4-methylthio-2-[(2-n-pentylthiobenzthiazol-6-sulfonyl)amino] butyric amide

^{1}H NMR(300MHz, $CDCl_3$): δ 0.92(t, 3H), 1.41(m, 4H), 1.81(m, 2H), 1.9~2.1(m, 7H), 3.35(m, 2H), 3.9(s, 1H), 6.7(m, 1H), 7.86(s, 2H), 8.3(s, 1H), 10.1(s, 1H)

Example 32-7: (2R)-N-hydroxy-4-methylthio-2-[(2-n-hexylthiobenzthiazol-6-sulfonyl)amino] butyric amide

^{1}H NMR(300MHz, $CDCl_3$): δ 0.9(t, 3H), 1.3(m, 4H), 1.5(m, 2H), 1.83(m, 3H), 2.0(s, 3H), 2.1(m, 1H), 2.35(m, 2H), 3.37(t, 2H), 4.0(d, 1H), 6.6(d, 1H), 7.89(m, 2H), 8.3(s, 1H), 10.2(s, 1H)

Example 32-8: (2R)-N-hydroxy-4-methylthio-2-[(2-(cyclohexylmethylthio)benzthiazol-6-sulfonyl)amino]butyric amide

^{1}H NMR(300MHz, $CDCl_3$): δ 1.1(m, 2H), 1.23(m, 3H), 1.73(m, 9H), 1.91(m, 4H), 2.32(d, 2H), 4.0(d, 1H), 6.2(d, 1H), 7.9(M, 2H),

8.31(s, 1H), 9.4(s, 1H)

Example 32-9: (2R)-N-hydroxy-4-methyl-2-[(2-n-pentylthiobenzthiazol-6-sulfonyl)amino] valeric amide

^{1}H NMR(300MHz, $CDCl_3$): δ 0.64(m, 3H), 0.87(m, 6H), 1.4~1.8(m, 9H), 3.31(t, 2H), 3.8(d, 1H), 6.4(d, 1H), 7.8(s, 2H), 8.3(s, 1H), 10.4(s, 1H)

Example 32-10: (2R)-N-hydroxy-4-methyl-2-[(2-n-hexyl-thiobenzthiazol-6-sulfonyl)amino]valeric amide

^{1}H NMR(300MHz, $CDCl_3$): δ 0.64~0.87(m, 9H), 1.3~1.78(m, 9H), 3.32(m, 2H), 3.8(m, 1H), 6.3(m, 1H), 7.83(s, 2H), 8.23(s, 1H), 10.2(s, 1H)

Example 33: Preparation of (2R)-2-[(2-n-pentylthio-benzthiazol-6-sulfonyl)benzylamino] propionic acid and other derivatives

(2R)-2-[(2-n-pentylthiobenzthiazol-6-sulfonyl) amino]propionic acid methylester(131mg, 0.325mmol) prepared in Example 29 was dissolved in DMF(1mL). K_2CO_3(135mg, 3equi.) and benzylbromide(0.05mL, 1.3equi.) were added at RT, and stirred for 1 hour at RT. When starting material was exhausted, ethylacetate(5mL) and H_2O were added to afford the phase separation. The separated organic phase was washed with H_2O for several times, dried over $MgSO_4$, distilled under reduced pressure to prepare the titled compound, (2R)-2-[(2-n-pentylthiobenzthiazol-6-sulfonyl)benzylamino] propionic acid methylester(160mg, 100%).

^{1}H NMR(300MHz, $CDCl_3$): δ 0.93(t, 3H), 1.31(d, 3H), 1.45(m, 4H), 1.85(p, 2H), 3.38(t, 2H), 3.42(s, 3H), 4.58(dd, 2H), 4.68(q, 1H), 7.26(m, 5H), 7.84(dd, 2H), 8.18(s, 1H)

The above prepared (2R)-2-[(2-n-pentylthiobenzthiazol-6-sulfonyl)benzylamino] propionic acid methylester(146mg, 0.296mmol) was dissolved in THF/H_2O(1mL/1mL). LiOH(62mg, 5equi.) was added and the reaction solution was refluxed for 5 to 7 days until starting material was disappeared. After the reaction was completed, the reaction solution was distilled under reduced pressure and treated with 1N HCl solution, and ethylacetate(5mL) was added. The separated organic phase containing extracted product was washed with NaCl solution, dried over $MgSO_4$ and distilled under reduced pressure. The remaining material after distillation was purified on silica gel chromatography using ethylacetate/n-hexane(1/1) and ethylacetate/dichloromethane/acetate(1/1/trace amount) as solvent. The purified compound was dried under vacuum to prepare the titled compound, (2R)-2-[(2-n-pentylthiobenzthiazol-6-sulfonyl)benzylamino] propionic acid(142mg, 100%).

^{1}H NMR(300MHz, $CDCl_3$): δ 0.94(t, 3H), 1.38~1.45(m, 7H), 1.83(p, 2H), 3.35(t, 2H), 4.42(d, 1H), 4.65(m, 2H), 7.28(m, 5H), 7.87(m, 2H), 8.20(s, 1H)

The following titled compounds were prepared by hydrolysis of n-benzyl intermediates, which were obtained by introducing benzyl group to nitrogen of amide of various methylesters as starting material prepared analogously as in Example 29, in a similar manner as above under LiOH/THF/H_2O condition.

Example 33-1: (2R)-2-[(2-(cyclohexylmethylthio) benzthiazol-6-sulfonyl)benzylamino] propionic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 1.0~1.28(m, 5H), 1.37(d, 3H), 1.78(m, 4H), 1.9(d, 2H), 3.23(d, 2H), 4.35(d, 1H), 4.65(m, 2H), 7,26(m, 5H), 7.85(m, 2H), 8.17(s, 1H)

Example 33-2: (2R)-2-[(2-n-pentylthiobenzthiazol-6-sulfonyl)benzylamino]-3-phenylpropionic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.92(t, 3H), 1.38(m, 4H), 1.83(p, 2H), 2.3(m, 2H), 2.9(m, 1H), 3.33(t, 2H), 4.5(dd, 2H), 5.9(s, 1H), 7.0(m, 10H), 7.73(dd, 2H), 8.0(s, 1H)

Example 33-3: (2R)-2-[(2-(cyclohexylmethylthio) benzthiazol-6-sulfonyl)benzylamino]-3-phenylpropionic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 1.24(m, 5H), 1.74(m, 4H), 1.9(m, 2H), 2.4(m, 2H), 2.9(m, 1H), 3.2(d, 2H), 4.4(dd, 2H), 4.8(m, 1H), 7.0(m, 2H), 7.2(m, 8H), 7.7(dd, 2H), 8.0(s, 1H)

Example 33-4: (2R)-4-methylthio-2-[(2-n-pentylthiobenz-thiazol-6-sulfonyl)benzylamino]butyric acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.93(t, 1H), 1.4(m, 4H), 1.7(m, 2H), 1.8(s, 1H), 2.1(m, 2H), 2.3(m, 2H), 3.3(t, 2H), 4.3(d, 1H), 4.7(m, 2H), 7.3(m, 5H), 7.86(s, 1H), 8.3(s, 1H)

Example 33-5: (2R)-4-methyl-2-[(2-n-pentylthiobenz-

thiazol-6-sulfonyl)benzylamino]valeric acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.55(d, 3H), 0.85(d, 3H), 0.93(t, 3H), 1.47(m, 7H), 1.83(p, 2H), 3.34(t, 2H), 4.4(d, 1H), 4.6(m, 1H), 4.72(d, 1H), 7.26(m, 3H), 7.37(m, 2H), 7.84(m, 2H), 8.18(s, 1H)

Example 34: Preparation of (2R)-N-hydroxy-2-[(2-n-pentylthiobenzthiazol-6-sulfonyl)benzylamino] propion amide and other derivatives

(2R)-2-[(2-n-pentylthiobenzthiazol-6-sulfonyl) benzylamino]propionic acid(157mg, 0.328mmol) prepared in Example 33 was dissolved in dichloromethane(2mL) and cooled down to 0℃. Oxalylchloride(0.114mL, 10equi.) and DMF of catalytic amount were added and the reaction solution was refluxed for 3 hours at RT. After reaction, the solution was distilled under reduced pressure to remove the solvent and dried under reduced pressure to give (2R)-3-methyl-2-[(2-methylthiobenzthiazol-6-sulfonyl)amino]butanoic chloride. The compound was then dissolved in THF(1mL) to obtain acid chloride THF solution. Hydroxyamine hydrochloride salt(0.23g, 10equi.) and $NaHCO_3$(0.33g, 12equi.) were dissolved in THF/H_2O(3mL/3mL) and cooled down to 0℃ to give a hydroxyamine solution. The above acid chloride THF solution was slowly added to the hydroxyamine solution at 0℃. After 1 hour, the solvent was removed from the reaction solution. Then, the product was extracted with ethylacetate(10mL), washed with H_2O and 0.1N HCl, dried over $MgSO_4$, distilled under reduced pressure and vacuum-dried to prepare the titled compound, (2R)-N-hydroxy-2-[(2-n-pentylthiobenzthiazol-6-sulfonyl)benzylamino] propionamide(163mg, 100%).

^{1}H NMR(300MHz, DMSO-d_6): δ 0.93(t, 3H), 1.23(m, 3H), 1.3(m, 4H), 1.85(p, 2H), 3.38(t, 2H), 4.3(d, 1H), 4.5(m, 1H), 4.7(d, 1H), 7.28(m, 5H), 7.8(dd, 2H), 8.2(s, 1H), 9.0(s, 1H)

Using various N-benzylsulfonyl acid derivatives as a starting material obtained in Example 33, the following titled compounds were prepared by applying the above method under the condition of oxalylchloride/hydroxyamine hydrochloride/$NaHCO_3$/THF/H_2O.

Example 34-1: (2R)-N-hydroxy-2-[(2-(cyclohexylmethyl-thio)benzthiazol-6-sulfonyl)benzylamino] propionamide

^{1}H NMR(300MHz, $CDCl_3$): δ 1.26(m, 8H), 1.74(m, 4H), 1.9(m, 2H), 3.28(d, 2H), 4.2(d, 1H), 4.4(m, 1H), 4.6(d, 1H), 7.3(m, 5H), 7.8(dd, 2H), 8.1(s, 1H), 9.0(s, 1H)

Example 34-2: (2R)-N-hydroxy-2-[(2-n-pentylthiobenz-thiazol-6-sulfonyl)benzylamino]-3-phenylpropionamide

^{1}H NMR(300MHz, $CDCl_3$): δ 0.94(t, 3H), 1.3(m, 4H), 1.86(p, 2H), 2.7(dd, 1H), 3.2(dd, 1H), 3.4(t, 2H), 4.6(dd, 2H), 6.8(m, 2H), 7.0(m, 3H), 7.3(m, 5H), 7.7(d, 1H), 7.8(d, 1H), 7.9(s, 1H), 9.0(s, 1H)

Example 34-3: (2R)-N-hydroxy-4-methylthio-2-[(2-n-pentylthiobenzthiazol-6-sulfonyl) benzylamino]butyric amide

^{1}H NMR(300MHz, $CDCl_3$): δ 0.9(t, 3H), 1.3(m, 7H), 1.8(m, 3H), 2.2(m, 2H), 3.38(t, 2H),

4.3(d, 1H), 4.6(m, 2H), 7.29(m, 5H),
7.8(dd, 2H), 8.1(s, 1H), 9.1(s, 1H)

Example 34-4: (2R)-N-hydroxy-4-methyl-2-[(2-n-pentylthiobenzthiazol-6-sulfonyl)benzyl-amino]valeric amide

^{1}H NMR(300MHz, $CDCl_3$): δ 0.64(dd, 6H), 0.93(t, 3H),
1.26(m, 1H), 1.4(m, 5H), 1.8(m, 3H),
3.83(t, 2H), 4.4(m, 2H), 4.65(d, 1H),
7.28(m, 5H), 7.7(d, 1H), 7.82(d, 1H),
8.0(s, 1H), 9.1(s, 1H)

Example 35: Preparation of (±)-diethyl-1-[(2-(n-butylthio)benzthiazol-6-sulfonyl) amino]-2-phenylethyl-phosphonate and other derivatives

Diethyl 1-amino-2-phenylethylphosphonate(0.14g, 0.5442mmol) prepared by the conventionally known method was dispersed in dichloromethane(3mL) and cooled down to 0℃, and triethylamine(0.08mL, 1.1equi.) was added. 2-n-butylthio-6-benzthiazolsulfonyl chloride(0.184g, 1.05equi.) prepared in the above Example was dissolved in dichloromethane(2mL) to give a dichloromethane solution. The dichloromethane solution was added while maintaining the temperature of 0℃. After 5 hours, when starting material was exhausted, the organic phase was washed with 1N HCl, dried over $MgSO_4$, distilled under reduced pressure and dried under vacuum to prepare the titled compound, diethyl-1-[(2-(n-butylthio)benzthiazol-6-sulfonyl)amino]-2-phenylethylphosphonate(0.206g, 70%).

Using 2-n-hexylthio-6-benzthiazolsulfonyl chloride (0.25g, 1.05equi.) and 2-(cyclohexylmethylthio)-6-benzthiazolsulfonyl chloride(0.177g, 1.05equi.) prepared by the same method as above, the following titled compounds were prepared.

Example 35-1: (±)-diethyl-1-[(2-(n-hexylthio) benzthiazol-6-sulfonyl)amino]-2-phenyl-ethylphosphonate

^{1}H NMR(300MHz, $CDCl_3$): δ 0.89(t, 3H), 1.35(t, 10H), 1.50(m, 2H), 1.83(p, 2H), 2.75(m, 1H), 3.1(m, 1H), 3.36(t, 2H), 4.07(m, 4H), 4.25(m, 1H), 6.85(d, 1H), 6.95(m, 5H), 7.65(dd, 2H), 7.86(s, 1H)

Example 35-2: (±)-diethyl-1-[(2-(n-butylthio) benzthiazol-6-sulfonyl)amino]-2-phenyl-ethylphosphonate

^{1}H NMR(300MHz, $CDCl_3$): δ 0.99(t, 3H), 1.3(q, 6H), 1.53(h, 2H), 1.83(p, 2H), 2.82(m, 1H), 3.1(m, 1H), 3.39(d, 2H), 4.10(m, 4H), 4.25(m, 1H), 6.65(d, 1H), 6.97(m, 5H), 7.68(dd, 2H), 7.87(s, 1H)

Example 35-3: (±)-diethyl-1-[(2-(cyclohexylmethylthio) benzthiazol-6-sulfonyl)amino]-2-phenylethylphosphonate

^{1}H NMR(300MHz, $CDCl_3$): δ 1.1(m, 2H), 1.26(m, 9H), 1.71(m, 4H), 1.93(d, 2H), 2.83(m, 1H), 3.11(m, 1H), 3.28(d, 2H), 4.09(m, 4H), 4.27(m, 1H), 6.78(d, 1H), 6.93(m, 5H), 7.67(dd, 2H), 7.86(s, 1H)

Example 36: Preparation of (±)-1-[(2-(n-butylthio) benzthiazol-6-sulfonyl)amino]-2-phenylethyl phosphonic acid and other derivatives

(±)-Diethyl-1-[(2-(n-butylthio)benzthiazol-6-sulfonyl)amino]-2-phenylethylphosphonate(0.1g,0.184mmol)

prepared in Example 35 was dissolved in anhydrous dichloromethane(3mL) under the anhydrous nitrogen. Then, bromotrimethylsilane(0.24mL, 10equi.) was added at 0℃ in the presence of nitrogen and the reaction temperature was slowly elevated to the room temperature, followed by stirring for 12 hours. When starting material was exhausted, the solvent was dried under reduced pressure and crystallized with cold water to give a solid compound which was then filtered. The compound thus obtained was washed with H_2O several times and dried under reduced pressure to prepare the titled compound, (±)-1-[(2-(n-butylthio)benzthiazol-6-sulfonyl)amino]-2-phenylethylphosphonic acid(80mg, 90%).

^{1}H NMR(300MHz, $CDCl_3$): δ 1.0(t, 3H), 1.53(m, 2H), 1.85(m, 2H), 2.7(m, 1H), 3.0(m, 1H), 3.4(t, 2H), 4.0(m, 1H), 6.9(m, 5H), 7.67(m, 2H), 7.8(s, 1H)

The following titled compounds were prepared in a similar manner as above, except for employing (±)-diethyl-1-[(2-(n-hexylthio)benzthiazol-6-sulfonyl)amino]-2-phenylethylphosphonate(0.05g, 0.087mmol) and (±)-diethyl-1-[(2-(cyclohexylmethylthio)benzthiazol-6-sulfonyl)amino]-2-phenylethylphosphonate(0.05g, 0.0858 mmol) prepared in Example 35 as starting materials.

Example 36-1: (±)-1-[(2-(n-hexylthio)benzthiazol-6-sulfonyl)amino]-2-phenylethylphosphonic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.91(t, 3H), 1.35(m, 4H), 1.50(m, 2H), 1.89(p, 2H), 2.7(m, 1H), 3.0(m, 1H), 3.4(t, 2H), 4.0(m, 1H), 6.88(m, 5H), 7.5(d, 1H), 7.68(d, 1H), 7.7(s, 1H)

Example 36-2: (±)-1-[(2-(cyclohexylmethylthio) benzthiazol-6-sulfonyl)amino]-2-phenyl-ethylphosphonic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 1.17(m, 2H), 1.28(m, 3H), 1.79(m, 4H), 1.95(d, 2H), 2.7(m, 1H), 3.1(m, 1H), 3.33(d, 2H), 4.09(m, 1H), 6.86(m, 5H), 7.6(d, 1H), 7.73(d, 1H), 7.83(s, 1H)

Example 37: (2R)-N-[2-(n-pentylthiobenzthiazol-6-sulfonyl)]-2-methylcarboxylpyrrolidine

(D)-proline methylester hydrochloride(0.29g, 1.75mmol) was dispersed in dichloromethane(3mL) and cooled down to 0℃, and triethylamine(0.73mL, 3equi.) was added. 2-n-pentylthio-6-benzthiazolsulfonyl chloride (0.35g, 1.0equi.) prepared in Example 2 was dissolved in dichloromethane(2mL) to give a dichloromethane solution. Then, the dichloromethane solution was added while maintaining the temperature of 0℃. After starting material was exhausted(about 5 hours), the organic phase was washed with 1N HCl, dried over $MgSO_4$, distilled under reduced pressure and dried under vacuum to prepare (2R)-N-[2-(n-pentylthiobenzthiazol-6-sulfonyl)]-2-methylcarboxyl- pyrrolidine(0.17g, 23%).

^{1}H NMR(300MHz, $CDCl_3$): δ 0.93(t, 3H), 1.45(m, 4H), 1.84(m, 3H), 2.0(m, 3H), 3.37(t, 3H), 3.5(m, 1H), 3.7(s, 3H), 4.4(t, 1H), 7.9(m, 2H), 8.3(s, 1H)

Example 38: (2R)-N-[2-(n-pentylthiobenzthiazol-6-sulfonyl)]-2-pyrrolidylcarboxylic acid

(2R)-N-[2-(n-pentylthiobenzthiazol-6-sulfonyl)]-2-methylcarboxylpyrrolidine(0.17g, 0.4mmol) prepared in

Example 37 was dissolved in THF/H_2O(2mL/2mL), and added LiOH(0.083g, 5equi.). After reacting with reflux for 6 hours, the solution was distilled under reduced pressure and treated with 1N HCl, and extracted with ethylacetate(10mL). The extracted product was washed with NaCl solution, dried over $MgSO_4$, distilled under reduced pressure and dried under vacuum to prepare the titled compound, (2R)-N-[2-(n-pentylthiobenzthiazol-6-sulfonyl)]-2-pyrrolidylcarboxylic acid(160mg, 97%).

^{1}H NMR(300MHz, $CDCl_3$): δ 0.93(t, 3H), 1.45(m, 4H), 1.82(m, 3H), 1.83(m, 2H), 2.15(m, 1H), 3.3(m, 1H), 3.38(t, 2H), 3.6(m, 1H), 4.35(m, 1H), 7.95(dd, 2H), 8.3(s, 1H)

Example 39: (2R)-N-[2-(n-hexylthiobenzthiazol-6-sulfonyl)]-2-pyrrolidylcarboxylic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.90(t, 3H), 1.33(m, 4H), 1.49(m, 2H), 1.8(m, 3H), 1.87(m, 2H), 2.2(m, 1H), 3.3(q, 1H), 3.38(t, 2H), 3.6(m, 1H), 4.3(m, 1H), 7.95(dd, 2H), 8.3(s, 1H)

Example 40: Preparation of (3R)-1,2,3,4-tetrahydro-N-[2-(n-pentylthiobenzthiazol-6-sulfonyl)]-3-isoquinolinecarboxylic acid

(3R)-1,2,3,4-Tetrahydro-3-isoquinolinecarboxylic acid(0.2g, 1mmol) prepared by the conventionally known method was dispersed in dichloromethane(3mL) and cooled down to 0℃, and triethylamine(0.4mL, 3equi.) was added. 2-n-pentylthio-6-benzthiazolsulfonyl chloride(0.26g, 1.0equi.) prepared in Example 2 was dissolved in dichloromethane(2mL) to give a dichloromethane solution. Then, the dichloromethane solution was added while maintaining the temperature of 0℃. After starting

material was exhausted(about 5 hours), the solution was treated with 1N HCl solution and then, the organic phase was washed with NaCl solution, dried over $MgSO_4$, distilled under reduced pressure and dried under vacuum to prepare the titled compound, (3R)-1,2,3,4-tetrahydro-N-[2-(n-pentylthiobenzthiazol-6-sulfonyl)]-3-isoquinoline-carboxylic acid(0.3g, 63%).

^{1}H NMR(300MHz, $CDCl_3$): δ 0.92(t, 3H), 1.4(m, 4H), 1.83(m, 2H), 3.18(d, 2H), 3.35(t, 2H), 4.6(dd, 2H), 5.0(t, 1H), 7.15(m, 4H), 7.83(m, 2H), 8.25(s, 1H)

Example 41: Preparation of (±)-1,2,3,4-tetrahydro-N-[2-(n-pentylthiobenzthiazol-6-sulfonyl)]-3-methyl-3-isoquinolinecarboxylic acid methyl-ester

(±)-1,2,3,4-tetrahydro-3-methyl-3-isoquinoline-carboxylic acid methylester(0.16g, 0.78mmol) prepared by the conventionally known method was dispersed in dichloromethane(3mL) and cooled down to 0℃, and triethylamine(0.73mL, 3equi.) was added. 2-n-pentylthio-6-benzthiazolsulfonyl chloride (0.35g, 1.0equi.) prepared in Example 2 was dissolved in dichloromethane(2mL) to give a dichloromethane solution. Then, the dichloromethane solution was added while maintaining the temperature of 0℃. After starting material was exhausted(about 5 hours), the organic phase was washed with 1N HCl, dried over $MgSO_4$, distilled under reduced pressure and dried under vacuum, to prepare the titled compound, (±)-1,2,3,4-tetrahydro-N-[2-(n-pentylthiobenzthiazol-6-sulfonyl)]-3-methyl-3-isoquinolinecarboxylic acid methylester(0.17g, 23%).

^{1}H NMR(300MHz, $CDCl_3$): δ 0.93(t, 3H), 1.45(m, 4H), 1.58(s, 3H), 1.84(m, 2H), 2.88(d, 1H),

3.25(d, 1H), 3.36(t, 2H), 3.80(s, 3H),
4.4(dd, 2H), 7.2(m, 4H), 7.89(m, 2H),
8.3(s, 1H)

Example 42: Preparation of (±)-1,2,3,4-tetrahydro-N-[2-(n-pentylthiobenzthiazol-6-sulfonyl)]-3-methyl-3-isoquinolinecarboxylic acid

(±)-1,2,3,4-tetrahydro-N-[2-(n-pentylthiobenzthiazol-6-sulfonyl)]-3-methyl-3-isoquinolinecarboxylic acid methylester(0.17g, 0.337mmol) was dissolved in THF/H_2O(2mL/2mL), and LiOH(0.071g, 5equi.) was added. After the reaction soluton was reacted with reflux for 6 hours, the solvent was distilled under reduced pressure and treated with 1N HCl, and extracted with ethylacetate(10mL). The material thus extracted was washed with NaCl solution, dried over $MgSO_4$, distilled under reduced pressure and dried under vacuum to prepare the titled compound, (±)-1,2,3,4-tetrahydro-N-[2-(n-pentylthiobenzthiazol-6-sulfonyl)]-3-methyl-3-isoquinolinecarboxylic acid(100mg, 60%).

^{1}H NMR(300MHz, $CDCl_3$): δ 0.93(t, 3H), 1.45(m, 4H),
1.64(s, 3H), 1.84(m, 2H), 2.96(d, 1H),
3.31(d, 1H), 3.37(t, 2H), 4.4(dd, 2H),
7.0(d, 4H), 7.20(m, 3H), 7.91(m, 2H),
8.33(s, 1H)

Example 43: Preparation of (3S)-4-(2-cyclohexyl-methylthiobenzthiazol-6-sulfonyl)-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxylic acid

(3S)-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxylic acid(0.93g, 5.31mmol) prepared by the conventionlly known method(see: WO 9720824) was dissolved in DMF(7mL). DBU(0.95mL, 1.2equi.) was added

and the reaction solution was stirred for 1 hour at RT. Then, dimethylthexylsilyl chloride(1.15mL, 1.1equi.) was added and the reaction solution was stirred for 5 hours at RT. The reaction solution was added to ice water/hexane:t-butylmethylether(7mL:7mL) solution, followed by weak shaking. The organic phase was dried over $MgSO_4$, distilled under reduced pressure and dried under a vacuum to give (3S)-dimethylthexylsilyl-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxylate(1.5g) in a liquid form. It was dissolved in EDC(15mL) and cooled down to 0°C. N-methylmorpholine(0.62mL, 1.2equi.) was added, followed by stirring for 30 minutes. 2-cyclohexylmethylthio-6-benzthiazolsulfonyl chloride(1.7g, 1equi.) was dissolved in EDC(5mL) and then, the solution was added to the reaction mixture. After starting material was exhausted, the product was extracted with ethylacetate(10mL). The material thus extracted was washed with NaCl solution, dried over $MgSO_4$, distilled under reduced pressure and dried under vacuum to give (3S)-4-(2-cyclohexylmethylthiobenzthiazol-6-sulfonyl)-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxylic acid dimethylthexylsilyl ester. The compound was dissolved in methanol(20mL) and the solution was refluxed for 6 hours. Then, the solvent was distilled under reduced pressure and the pH was adjusted to 2 with 2N HCl, and extracted with ethylacetate(10mL). The material thus extracted was dried over $MgSO_4$, distilled under reduced pressure and dried under vacuum. A remaining mixture was purified on silica gel chromatography by elution with ethylacetate/hexane(1/5) to give the titled compound, (3S)-4-(2-cyclohexylmethylthiobenzthiazol-6-sulfonyl)-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxylic acid(1.08g, 40%).

^1H NMR(300MHz, $CDCl_3$): δ 1.1(m, 2H), 1.25(m, 4H), 1.37(s, 3H), 1.64(s, 3H), 1.74(m, 3H),

1.9(m, 2H), 2.5(d, 1H), 3.15(m, 1H),
3.21(d, H), 3.7(m, 1H), 4.12(m, 1H),
4.47(s, 1H), 7.74(d, 1H), 7.84(d, 1H),
8.2(s, 1H)

Example 44: Preparation of (3S)-4-[2-(n-butylthiobenz-thiazol-6-sulfonyl)]-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxylic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.98(t, 3H), 1.38(s, 3H),
1.53(m, 2H), 1.65(s, 3H), 1.82(m, 2H),
2.5(d, 1H), 3.15(m, 1H), 3.33(t, 2H),
3.7(m, 1H), 4.1(d, 1H), 4.5(s, 1H),
7.75(d, 1H), 7.87(d, 1H), 8.2(s, 1H)

Example 45: Preparation of (3S)-4-[2-(n-hexylthiobenz-thiazol-6-sulfonyl)]-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxylic acid

^{1}H NMR(300MHz, $CDCl_3$): δ 0.92(t, 3H), 1.38(m, 4H),
1.39(s, 3H), 1.50(m, 2H), 1.67(s, 3H),
1.82(m, 2H), 2.5(d, 1H), 3.2(m, 1H),
3.31(t, 2H), 3.75(m, 1H), 4.16(d, 1H),
4.5(s, 1H), 7.77(d, 1H), 7.89(d, 1H),
8.22(s, 1H)

Example 46: Preparation of (2R)-N-hydroxy-1-[2-(n-pentylthiobenzthiazol-6-sulfonyl)]-2-pyrrolidylcarboxylamide

(2R)-N-[2-(n-pentylthiobenzthiazol-6-sulfonyl)]-2-pyrrolidylcarboxylic acid(0.16g, 0.39mmol) prepared in Example 38 was dissolved in dichloromethane(2mL) and cooled down to 0℃. Oxalylchloride(0.1mL, 3equi.) and DMF of catalytic amount was added, and reacted for 3 hours at RT. Then, the reaction solution was distilled under reduced pressure to remove solvent and dried under

reduced pressure. And then, the remaining material was dissolved in THF(1mL). Hydroxylamine hydrochloride(0.27g, 10equi.) and $NaHCO_3$(0.39g, 12equi.) were dissolved in THF/H_2O(2mL/2mL) and cooled down to 0℃. The acid chloride/THF solution thus obtained was slowly added to hydroxylamine solution while maintaining the temperature of 0℃. After 1 hour, the solvent was removed from the reaction solution. The product was extracted with ethylacetate(5mL) and then, washed with H_2O and 0.1N HCl, dried over $MgSO_4$, distilled under reduced pressure and dried under vacuum to prepare the titled compound, (2R)-N-hydroxy-1-[2-(n-pentylthiobenzthiazol-6-sulfonyl)]-2-pyrrolidylcarboxylic acid(0.14g, 84%).

^{1}H NMR(300MHz, $CDCl_3$): δ 0.93(t, 3H), 1.43(m, 4H), 1.6(m, 2H), 1.8(m, 4H), 2.2(m, 1H), 3.2(m, 1H), 3.37(t, 2H), 3.6(m, 1H), 4.2(d, 1H), 7.94(dd, 2H), 8.3(s, 1H), 9.5(s, 1H)

Example 47: Preparation of (2R)-N-hydroxy-1-[2-(n-hexylthiobenzthiazol-6-sulfonyl)]-2-pyrrolidyl-carboxylamide

^{1}H NMR(300MHz, $CDCl_3$): δ 0.9(t, 3H), 1.33(m, 4H), 1.45(m, 2H), 1.6(m, 2H), 1.8(m, 3H), 2.2(m, 1H), 3.2(m, 1H), 3.38(t, 2H), 3.6(m, 1H), 4.2(d, 1H), 7.94(dd, 2H), 8.3(s, 1H), 9.5(s, 1H)

Example 48: Preparation of (3R)-N-hydroxy-1,2,3,4-tetrahydro-2-[2-(n-pentylthiobenzthiazol-6-sulfonyl)]-3-isoquinolinecarboxylamide

(3R)-1,2,3,4-tetrahydro-2-[2-(n-pentylthiobenz-thiazol-6-sulfonyl)]-3-isoquinolinecarboxylic acid(0.2g, 0.42mmol) prepared in Example 40 was dissolved in

dichloromethane(2mL) and cooled down to 0℃. Oxalylchloride(0.11mL, 3equi.) and DMF of catalytic amount was added, and reacted for 3 hours at RT. Then, the reaction solution was distilled under reduced pressure to remove solvent and dried under reduced pressure. And then, the remaining material was dissolved in THF(1mL). Hydroxylamine hydrochloride(0.29g, 10equi.) and $NaHCO_3$(0.42g, 12equi.) were dissolved in THF/H_2O(2mL/2mL) and cooled down to 0℃. The acid chloride/THF solution thus obtained was slowly added to hydroxylamine solution while maintaining the temperature of 0℃. After 1 hour, the solvent was removed from the reaction solution. The product was extracted with ethylacetate(5mL) and then, washed with H_2O and 0.1N HCl, dried over $MgSO_4$, distilled under reduced pressure and dried under vacuum to prepare (3R)-N-hydroxy-1,2,3,4-tetrahydro-2-[2-(n-pentylthio-benzthiazol-6-sulfonyl)]-3-isoquinolinecarboxylamide (0.2g, 99%).

^{1}H NMR(300MHz, $CDCl_3$): δ 0.92(t, 3H), 1.41(m, 4H), 1.8(m, 2H), 2.65(m, 1H), 3.15(m, 1H), 3.35(t, 2H), 4.5(m, 3H), 7.09(m, 4H), 7.8(dd, 2H), 8.16(s, 1H), 9.4(s, 1H)

Example 49: Preparation of (±)-N-hydroxy-1,2,3,4-tetrahydro-2-[2-(n-pentylthiobenzthiazol-6-sulfonyl)]-3-methyl-3-isoquinoline-carboxylamide

^{1}H NMR(300MHz, $CDCl_3$): δ 0.93(t, 3H), 1.40(m, 4H), 1.65(s, 3H), 1.83(m, 2H), 2.85(d, 1H), 3.24(d, 1H), 3.38(t, 2H), 4.42(d, 1H), 4.55(d, 1H), 7.24(m, 4H), 7.87(m, 2H), 8.28(s, 1H), 8.8(s, 1H)

Example 50: Preparation of (3S)-N-hydroxy-4-(2-cyclohexylmethylthiobenzthiazol-6-sulfonyl)-

2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxylamide

(3S)-4-(2-cyclohexylmethylthiobenzthiazol-6-sulfonyl)-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxylic acid(0.84g, 1.68mmol) prepared in Example 43 was dissolved in dichloromethane(2mL) and cooled down to 0℃. Oxalylchloride(0.44mL, 3equi.) and DMF of catalytic amount were added, and reacted for 3 hours at RT. Then, the reaction solution was distilled under reduced pressure to remove solvent and dried under reduced pressure. And then, the remaining material was dissolved in THF(1mL). Hydroxylamine hydrochloride(1.17g, 10equi.) and $NaHCO_3$(1.69g, 12equi.) were dissolved in THF/H_2O(2mL/2mL) and cooled down to 0℃. The acid chloride/THF solution thus obtained was slowly added to hydroxylamine solution while maintaining the temperature of 0℃. After 1 hour, the solvent was removed from the reaction solution. The product was extracted with ethylacetate(5mL) and then, washed with H_2O and 0.1N HCl, dried over $MgSO_4$, distilled under reduced pressure and dried under vacuum to prepare the titled compound, (3R)-N-hydroxy-1,2,3,4-tetrahydro-2-[2-(n-pentylthiobenzthiazol-6-sulfonyl)]-3-isoquinolinecarboxylamide(0.87g, 100%).

^{1}H NMR(300MHz, $CDCl_3$): δ 1.22(m, 5H), 1.28(s, 3H), 1.58(s, 3H), 1.74(m, 4H), 1.9(d, 2H), 2.45(d, 1H), 3.1(m, 1H), 3.28(d, 2H), 3.8(m, 2H), 4.3(s, 1H), 7.77(d, 1H), 7.87(d, 1H), 8.21(s, 1H), 10.8(s, 1H)

Example 51: Preparation of (3S)-N-hydroxy-4-[2-(n-butylthiobenzthiazol-6-sulfonyl)]-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxylamide

^{1}H NMR(300MHz, $CDCl_3$): δ 0.98(t, 3H), 1.29(s, 3H),

1.53(m, 4H), 1.60(s, 3H), 1.83(m, 2H),
2.5(d, 1H), 3.2(m, 2H), 3.38(t, 2H),
4.1(d, 1H), 4.6(s, 1H), 7.1(s, 1H),
7.8(d, 1H), 7.9(d, 1H), 8.23(s, 1H),
9.7(s, 1H)

Example 52: Preparation of (3S)-N-hydroxy-4-[2-(n-hexylthiobenzthiazol-6-sulfonyl)]-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxylamide

^{1}H NMR(300MHz, $CDCl_3$): δ 0.93(t, 3H), 1.26(s, 3H),
1.35(m, 4H), 1.5(m, 2H), 1.58(s, 3H),
1.9(m, 2H), 2.5(d, 1H), 3.1(m, 1H),
3.37(m, 3H), 3.78(t, 2H), 4.0(d, 1H),
4.53(s, 1H), 7.8(dd, 2H), 8.2(s, 1H),
9.9(s, 1H)

Example 53: (±)-methyl 2-amino-3-(4-biphenyl)propionate hydrochloride

Sodium(0.624g, 27mmol) was completely dissolved in absolute ethanol and diethyl acetamidomalonate(5.9g, 27mmol) was added in a solid form, followed by stirring for 1 hour. And then, 4-phenylbenzyl chloride(5g, 24.67mmol) and KI(0.1equi.) was added and a reaction was accomplished at a temperature of 50-60°C for 12 hours. After starting material, 4-phenylbenzyl chloride was completely exhausted, the solvent was distilled under reduced pressure and extracted with water/ethylacetate(100mL/100mL). The separated organic phase was washed with 1N HCl, dried over anhydrous $MgSO_4$, dried under reduced pressure to prepare acetamido (4-biphenylmethyl)malonic acid diethylester(9.1g, 96%).

^{1}H NMR(300MHz, DMSO-d_6): δ 1.19(t, 6H), 1.98(s, 3H),
3.48(s, 2H), 4.19(q, 4H), 7.07(d, 2H),

7.48(d, 2H), 7.65(m, 5H), 8.17(s, 1H)

5N-NaOH(5mL, 1.05equi.) was added to acetamido(4-biphenylmethyl)malonic acid diethylester(9.1g, 23.73mmol) and hydrolyzed at RT. Then, the solvent was removed from the reaction solution and impurities was removed by adding ethylacetate(20mL). And then, the solid product was obtained by filtering, washed several times with water and dried under reduced pressure to give 2-ethylcarboxy-2-acetylamino-3-(4-biphenyl) propionic acid(6.7g, 79%).

^{1}H NMR(300MHz, DMSO-d_6): δ 1.17(t, 3H), 1.95(s, 3H), 3.48(dd, 2H), 4.13(q, 2H), 7.07(d, 2H), 7.34(t, 1H), 7.45(t, 2H), 7.61(dd, 4H), 7.91(s, 1H)

2-Ethylcarboxy-2-acetylamino-3-(4-biphenyl) propionic acid(6.7g, 18mmol) was dissolved in toluene(40mL) and reacted with reflux for 6 hours to complete decarboxylation. After starting material was exhausted, the solvent was removed from the reaction soluton. The remaining material was redissolved in ethylacetate(50mL), washed with a saturated $NaHCO_3$(20mL), dried over anhydrous $MgSO_4$, dried under reduced pressure to parepare 2-acetylamino-3-(4-biphenyl)propionic acidethylester(4.4g, 79%).

^{1}H NMR(300MHz, $CDCl_3$): δ 1.28(t, 3H), 2.0(s, 3H), 3.16(d, 2H), 4.21(q, 2H), 4.91(q, 1H), 5.97(d, 1H), 7.18~7.71(m, 9H)

2-Acetylamino-3-(4-biphenyl)propionic acidethyl-ester(4.4g, 14.1mmol) was added to 6N-HCl solution and reacted with reflux for 12 hours. Then, the solution was cooled down to RT and filtered to obtain a solid which was then washed with water and dried under reduced

pressure finally to prepare 2-amino-3-(4-biphenyl)propionic acid hydrochloride(3.2g, 82%).

^{1}H NMR(300MHz, DMSO-d_6): δ 3.05(dd, 1H), 3.20(dd, 1H), 3.84(t, 1H), 7.37(m, 3H), 7.47(t, 2H), 7.65(m, 4H)

2-Amino-3-(4-biphenyl)propionic acid hydrochloride (3.2g, 11.6mmol) was dissolved in methanol and cooled down at 0°C. And, thionyl chloride(4.53mL, 5equi.) was slowly added and the temperature was elevated to RT. And then, the solution was stirred for 12 hours and the solvent was removed from the solution to give a solid, which was dispersed in diisopropyl ether, stirred for 1 hour and filtered, finally to prepare methyl 2-amino-3-(4-biphenyl)propionate hydrochloride(3.3g, 98%).

^{1}H NMR(300MHz, DMSO-d_6): δ 3.14(t, 2H), 3.72(s, 3H), 4.37(t, 1H), 7.37(m, 3H), 7.47(t, 2H), 7.66(m, 4H), 8.41(bs, 2H)

Example 54: (±)-2-Amino-3-(2-phenylthiazole-4-yl) propionic acid dihydrochloride

The titled compound, 2-amino-3-(2-phenylthiazole-4-yl)propionic acid dihydrochloride(0.52g, 20%) was prepared in a similar manner as in Example 14, except for employing diethyl acetamidomalonate(1.76g, 8.1mmol) and 2-phenylthiazole-5-methylchloride(1.54g, 7.35mmol).

^{1}H NMR(300MHz, DMSO-d_6): δ 2.72(m, 2H), 4.35(m, 1H), 7.50(m, 4H), 7.95(m, 2H), 8.30(bs, 2H)

Example 55: (±)-2-amino-3-(imidazo[1,2-a]pyridine-3-yl) propionic acid trihydrochloride

The titled compound, 2-amino-3-(imidazo[1,2-

a]pyridine-3-yl)propionic acid trihydrochloride (1.38g, 22%), was prepared in a similar manner as in Example 14, except for employing diethyl acetamidomalonate(4.78g, 22mmol) and imidazo[1,2-a]pyridine-3-methylchloride (3.33g, 20mmol).

^{1}H NMR(300MHz, DMSO-d_6): δ 3.5(m, 2H), 4.48(t, 1H), 7.49(m, 1H), 7.96(m, 2H), 8.28(s, 1H), 8.98(d, 1H)

Example 56: (±)-2-amino-4-phenylbutyric acid methylester hydrochloride

Sodium(0.515g, 1.1equi.) was completely dissolved in absolute ethanol and N-(*t*-butoxycarbonylamino)malonic acid diethylester(5.6g, 20.37mmol) was added, followed by stirring for 1 hour. Then, phenethyl bromide(3.06mL, 1.1equi.) and KI(0.1equi.) were added and reacted at a temperature of 50-60°C for 12 hours. After starting material, phenethyl bromide, was completely exhausted, the solvent was distilled under reduced pressure and the product was extracted with water/ethylacetate (100mL/100mL). Then, the separated organic phase was washed with 1N HCl, dried over anhydrous $MgSO_4$ and dried under reduced pressure to give N-(*t*-butoxycarbonyl)amino-2-phenethylmalonic acid diethylester. Without purification, both of the two esters were hydrolyzed with 5N-NaOH aqueous solution(5equi.) and the compound was decarbonated in 1,4-dioxane, finally to prepare 2-N-(*t*-butoxycarbonyl) amino-4-phenylbutyric acid(4.18g, 75%).

^{1}H NMR(300MHz, $CDCl_3$): δ 1.45(s, 9H), 1.98(m, 1H), 2.19(m, 1H), 2.72(t, 2H), 4.0(m, 1H), 4.35(m, 1H), 5.0(bs, 1H), 7.19(m, 3H), 7.29(m, 2H)

2-N-(*t*-butoxycarbonyl)amino-4-phenylbutyric acid(4.18g, 15mmol) was dissolved in methanol and cooled down to 0°C and thionyl chloride(5.9mL, 5equi.) was slowly added. Then, the temperature was elevated to RT and the solution was stirred for 12 hours. The solvent was removed from the solution to give a solid product, which was then dispersed in diisopropyl ether, stirred for 1 hour and filtered, finally to prepare 2-amino-4-phenylbutyric acid methylester hydrochloride(2.9g, 85%).

^{1}H NMR(300MHz, D_2O): δ 2.15(m, 2H), 2.66(m, 2H), 3.72(s, 3H), 4.04(t, 1H), 7.18(m, 3H), 7.27(m, 2H)

Example 57: (±)-2-amino-5-phenylvaleric acid methylester

Sodium(0.49g, 1.1equi.) was completely dissolved in absolute ethanol and N-(*t*-butoxycarbonylamino)malonic acid diethylester(5.33g, 19.35mmol) was added in a solid form, followed by stirring for 1 hour. Then, phenylpropyl bromide(3.23mL, 1.1equi.) and KI(0.1equi.) were added and reacted at a temperature of 50-60°C for 12 hours. After starting material, phenylpropyl bromide, was completely exhausted, the solvent was distilled under reduced pressure and the product was extracted with water/ethylacetate(100mL/100mL). Then, the separated organic phase was washed with 1N HCl, dried over anhydrous $MgSO_4$ and dried under reduced pressure to give 2-N-(*t*-butoxycarbonyl)amino-5-phenylvaleric acid (4.5g, 80%). Without purification, both of the two esters were hydrolyzed with 5N-NaOH aqueous solution(5equi.) and the compound was decarbonated in 1,4-dioxane to prepare 2-N-(*t*-butoxycarbonyl)amino-5-phenylvaleric acid(4.5g, 80%).

^{1}H NMR(300MHz, $CDCl_3$): δ 1.43(s, 9H), 1.68(m, 3H), 1.90(m, 1H), 2.63(m, 2H), 3.96(m, 1H),

4.34(m, 1H), 4.97(m, 1H), 7.18(m, 3H),
7.28(m, 2H)

2-N-(*t*-butoxycarbonyl)amino-5-phenylvaleric acid (4.5g, 15.48mmol) was dissolved in methanol and cooled down to 0°C, and thionyl chloride(6mL, 5equi.) was slowly added. Then, the temperature was elevated to RT and the solution was stirred for 12 hours. The solvent was removed from the solution to give a solid product, which was then dispersed in diisopropyl ether, stirred for 1 hour and filtered, finally to prepare 2-amino-5-phenylvaleric acid methylester hydrochloride(3.2g, 85%).

^{1}H NMR(300MHz, D_2O): δ 1.6(m, 2H), 1.83(m, 2H),
2.58(t, 2H), 3.72(s, 3H), 4.02(t, 1H),
7.16(m, 3H), 7.26(m, 2H)

Example 58: (D)-3-(4-allyloxyphenyl)-2-aminopropionic acid methylester hydrochloride

(D)-N-*t*-Butylcarboxytyrosine methylester(5.6g, 19mmol) was dissolved in acetone(60mL). K_2CO_3(3.92g, 1.5equi.) and KI(0.314g, 0.1equi.) were added to the solution and then, allyl bromide(1.7mL, 1.2equi.) was slowly added. Then, the reaction solution was refluxed for 12 hours. After starting material was completely exhausted, the solvent was distilled under reduced pressure and the product was extracted with water/ethylacetate(100mL/100mL). The organic phase was washed with water, dried over anhydrous $MgSO_4$ and dried under reduced pressure to give (D)-3-(4-allyloxyphenyl)-2-(N-*t*-butylcarboxy)aminopropionic acid methylester(6g, 95%). Without purification, the compound was dissolved in ethylacetate(50mL) and cooled down to 0°C and then, passed through by anhydrous HCl(5equi.) gas. After leaving to stand at RT for 5 hours, the solution was filtered to give a solid, which was then dried under

reduced pressure finally to prepare (D)-3-(4-allyloxyphenyl)-2-aminopropionic acid methylester hydrochloride(3.9g, 79%).

^{1}H NMR(300MHz, D_2O): δ 3.13(m, 2H), 3.74(s, 3H), 4.30(m, 1H), 4.53(m, 2H), 5.22(d, 1H), 5.33(d, 1H), 6.04(m, 1H), 6.92(d, 2H), 7.13(d, 2H)

Example 59: (D)-3-(4-Propargyloxyphenyl)-2-amino-propionic acid methylester hydrochloride

(D)-N-*t*-butylcarboxytyrosine methylester(4.35g, 14.7mmol) was dissolved in acetone(60mL). K_2CO_3(3.04g, 1.5equi.) and KI(0.24g, 0.1equi.) were added to the solution and then, propargyl bromide(1.97mL, 1.2equi.) was slowly added. Then, the reaction solution was refluxed for 12 hours. After starting material was completely exhausted, the solvent was distilled under reduced pressure and the product was extracted with water/ethylacetate(100mL/100mL). The organic phase was washed with water, dried over anhydrous $MgSO_4$ and dried under reduced pressure to give (D)-3-(4-propargyloxyphenyl)-2-(N-*t*-butylcarboxy) aminopropionic acid methylester(4.9g, 100%). Without purification, the compound was dissolved in ethylacetate(50mL) and cooled down to 0°C and then, passed through anhydrous HCl(5equi.) gas. After leaving to stand at RT for 5 hours, the solution was filtered to give a solid, which was then dried under reduced pressure to prepare (D)-3-(4-propargyloxyphenyl)-2-aminopropionic acid methylester hydrochloride(3.78g, 95%).

^{1}H NMR(300MHz, D_2O): δ 2.83(t, 1H), 3.16(dd, 1H), 3.21(dd, 1H), 3.73(s, 3H), 4.28(t, 1H), 6.97(d, 2H), 7.24(d, 2H)

Example 60: (D)-3-(4-benzyloxyphenyl)-2-aminopropionic acid methylester hydrochloride

(D)-N-*t*-butylcarboxytyrosine methylester(1.46g, 4.94mmol) was dissolved in acetone(20mL). K_2CO_3(1.02g, 1.5equi.) and KI(0.082g, 0.1equi.) were added to the solution and then, benzyl bromide(0.7mL, 1.2equi.) was slowly added. Then, the reaction solution was refluxed for 12 hours. After starting material was completely exhausted, the solvent was distilled under reduced pressure and the product was extracted with water/ethylacetate(100mL/100mL). The organic phase was washed with water, dried over anhydrous $MgSO_4$ and dried under reduced pressure to give (D)-3-(4-benzyloxyphenyl)-2-(N-*t*-butylcarboxy)aminopropionic acid methylester(1.9g, 100%). Without purification, the compound was dissolved in ethylacetate(20mL) and cooled down to 0°C and then, passed through anhydrous HCl(5equi.) gas. After leaving to stand at RT for 12 hours, the solution was filtered to give a solid, which was then dried under reduced pressure to prepare (D)-3-(4-benzyloxyphenyl)-2-aminopropionic acid methylester hydrochloride(1.48g, 93%).

^{1}H NMR(300MHz, D_2O): δ 3.08(dd, 1H), 3.14(dd, 1H), 3.71(s, 3H), 4.25(t, 1H), 5.07(s, 2H), 6.95(d, 2H), 7.11(d, 2H), 7.35(m, 5H)

Example 61: (D)-3-(4-(2-phenethyl)oxyphenyl)-2-amino-propionic acid methylester hydrochloride

(D)-N-*t*-butylcarboxytyrosine methylester(1.56g, 5.35mmol) was dissolved in acetone(20mL). K_2CO_3(1.11g, 1.5equi.) and KI(0.089g, 0.1equi.) were added to the solution and then, phenethyl bromide(0.88mL, 1.2equi.) was slowly added. Then, the reaction solution was refluxed for 48 hours. And then, the solvent was

distilled under reduced pressure and the product was extracted with water/ethylacetate(40mL/40mL). The organic phase was washed with water, dried over anhydrous $MgSO_4$, and then, purified on silica gel chromatography using ethylacetate/n-hexane(1/4) and dried under reduced pressure to give (D)-3-(4-(2-phenethyl)oxyphenyl)-2-(N-*t*-butylcarboxy)amino-propionic acid methylester(1.28g, 60%). The compound was dissolved in ethylacetate(20mL) and cooled down to 0°C and then, passed through anhydrous HCl(5equi.) gas. After leaving to stand at RT for 12 hours, the solution was filtered to give a solid, which was then dried under reduced pressure finally to prepare (D)-3-(4-(2-phenethyl)oxyphenyl)-2-aminopropionic acid methylester hydrochloride(1.08g, 100%).

^{1}H NMR(300MHz, D_2O): δ 2.99(t, 2H), 3.08(dd, 1H), 3.13(dd, 1H), 3.72(s, 3H), 4.23(t, 2H), 4.25(t, 1H), 6.87(d, 2H), 7.10(d, 2H), 7.25(m, 5H)

Example 62: (D)-3-(4-(3-phenyl-1-propyl)oxyphenyl)-2-aminopropionic acid methylester hydrochloride

(D)-N-*t*-butylcarboxytyrosine methylester(1.51g, 5.12mmol) was dissolved in acetone(20mL). K_2CO_3(1.06g, 1.5equi.) and KI(0.085g, 0.1equi.) were added to the solution and then, 3-phenyl-1-propane bromide(0.93mL, 1.2equi.) was slowly added. Then, the reaction solution was refluxed for 24 hours. After starting material was completely exhausted, the solvent was distilled under reduced pressure and the product was extracted with water/ethylacetate(40mL/40mL). The organic phase was washed with water, dried over anhydrous $MgSO_4$ and dried under reduced pressure to give (D)-3-(4-(3-phenyl-1-propyl)oxyphenyl)-2-(N-*t*-butylcarboxy)aminopropionic

acid methylester. Without purification, the compound was dissolved in ethylacetate(20mL) and cooled down to 0°C and then, passed through anhydrous HCl(5equi.) gas. After leaving to stand at RT for 12 hours, the solution was filtered to give a solid, which was then dried under reduced pressure finally to prepare (D)-3-(4-(3-phenyl-1-propyl)oxyphenyl)-2-aminopropionic acid methylester hydrochloride(0.9g, 50%).

^{1}H NMR(300MHz, D_2O): δ 1.99(p, 2H), 2.70(t, 2H), 3.08(dd, 1H), 3.13(dd, 1H), 3.71(s, 3H), 3.93(t, 2H), 4.24(t, 1H), 6.87(d, 2H), 7.10(d, 2H), 7.21(m, 5H)

Example 63: (D)-3-(4-(3-phthalimido-1-propyl)oxyphenyl)-2-aminopropionic acid methylester hydrochloride

(D)-N-t-butylcarboxytyrosine methylester(1.26g, 4.28mmol) was dissolved in acetone(20mL). K_2CO_3(0.89g, 1.5equi.) and KI(0.071g, 0.1equi.) were added to the solution and then, N-(3-bromopropyl)phthalimide(1.38g, 1.2equi.) was slowly added. Then, the reaction solution was refluxed for 12 hours. And then, the solvent was distilled under reduced pressure and the product was extracted with water/ethylacetate(40mL/40mL). The organic phase was washed with water, dried over anhydrous $MgSO_4$, and then, purified on silica gel chromatography using ethylacetate/n-hexane(1/2) and dried under reduced pressure to give (D)-3-(4-(3-phthalimido-1-propyl)oxyphenyl)-2-(N-*t*-butylcarboxy) aminopropionic acid methylester(1.34g, 65%). The compound was dissolved in ethylacetate(20mL) and cooled down to 0°C and then, passed through anhydrous HCl(5equi.) gas. After leaving to stand at RT for 12 hours, the solution was filtered to give a solid, which was then dried under reduced pressure finally to prepare

(D)-3-(4-(3-phthalimido-1-propyl)oxyphenyl)-2-aminopropionic acid methylester hydrochloride(1.07g, 92%).

^{1}H NMR(300MHz, D_2O): δ 2.04(p, 2H), 3.00(dd, 1H), 3.09(dd, 1H), 3.70(s, 3H), 3.76(t, 2H), 4.01(t, 2H), 4.19(t, 1H), 6.56(d, 2H), 6.96(d, 2H), 7.70(s, 4H)

Example 64: (2R)-2-[(2-heptylthiobenzthiazol-6-sulfonyl)amino]-3-(4-allyloxy)phenylpropionic acid

(D)-3-(4-allyloxyphenyl)-2-aminopropionic acid methylester hydrochloride(0.112g, 0.41mmol) prepared in Example 19 was dispersed in dichloromethane(10mL) and cooled down to 0℃ and then, triethylamine(0.17mL, 3equi.) was added. 2-n-Heptylthio-6-benzthiazolsulfonyl chloride(0.180g, 1.2equi.) prepared in Example 7 was dissolved in dichloromethane(2mL) to give a dichloromethane solution. Then, the dichloromethane solution was added while maintaining the temperature of 0℃. When starting material was disappeared after 5 hours, the organic phase was washed with 1N HCl solution, dried over anhydrous $MgSO_4$, distilled under reduced pressure and vacuum-dried to prepare (2R)-2-[(2-heptylthiobenzthiazol-6-sulfonyl)amino]-3-(4-allyloxy)phenylpropionic acid methylester(0.204g, 88%).

^{1}H NMR(300MHz, $CDCl_3$): δ 0.89(t, 3H), 1.3(m, 6H), 1.5(m, 2H), 1.8(p, 2H), 2.96(dq, 2H), 3.36(t, 2H), 3.48(s, 3H), 4.15(m, 1H), 4.46(m, 2H), 5.18(d, 1H), 5.27(d, 1H), 5.43(d, 1H), 6.05(m, 1H), 6.74(d, 2H), 6.94(d, 2H), 7.71(d, 1H), 7.85(d, 1H), 8.11(s, 1H)

(2R)-2-[(2-heptylthiobenzthiazol-6-sulfonyl)amino]-3-(4-allyloxy)phenylpropionic acid methylester(0.204g, 0.36mmol) was dissolved in THF/H_2O(2mL/2mL) and LiOH(0.076g, 5equi.) was added, and reacted with reflux for 12 hours. Then, the solution was distilled under reduced pressure and treated with 1N HCl. The product was extracted with ethylacetate(10mL). The separated organic phase was washed with NaCl solution, dried over anhydrous $MgSO_4$, distilled under reduced pressure and dried under vacuum to prepare the titled compound, (2R)-2-[(2-heptylthiobenzthiazol-6-sulfonyl)amino]-3-(4-allyloxy)phenylpropionic acid(0.71mg, 86%).

^{1}H NMR(300MHz, $CDCl_3$): δ 0.85(t, 3H), 1.28(m, 6H), 1.45(m, 2H), 1.80(m, 2H), 2.87(dd, 1H), 3.03(dd, 1H), 3.31(t, 2H), 4.16(m, 1H), 4.40(m, 2H), 5.25(d, 1H), 5.37(d, 1H), 5.77(d, 1H), 6.01(m, 1H), 6.66(d, 2H), 6.97(d, 2H), 7.71(d, 1H), 7.79(d, 1H), 8.04(s, 1H), 8.96(s, 1H)

Using (D)-3-(4-propargyloxyphenyl)-2-aminopropionic acid methylester hydrochloride obtained in Example 59, the following titled compound, (2R)-2-[(2-heptylthiobenzthiazol-6-sulfonyl)amino]-3-(4-propargyloxy)phenylpropionic acid, was prepared in a similar manner as aboves.

^{1}H NMR(300MHz, $CDCl_3$): δ 0.89(t, 3H), 1.29(m, 6H), 1.48(m, 2H), 1.83(m, 2H), 2.53(s, 1H), 2.91(dd, 1H), 3.00(dd, 1H), 3.35(m, 2H), 4.2(m, 1H), 4.63(s, 2H), 5.30(d, 1H), 6.79(d, 2H), 7.0(d, 2H), 7.70(d, 1H), 7.81(d, 1H), 8.10(s, 1H)

Using (D)-3-(4-benzyloxyphenyl)-2-aminopropionic acid methylester hydrochloride obtained in Example 60,

(2R)-2-[(2-heptylthiobenzthiazol-6-sulfonyl)amino]-3-(4-bentyloxyphenyl)propionic acid was prepared in a similar manner as aboves.

^{1}H NMR(300MHz, $CDCl_3$): δ 0.9(t, 3H), 1.30(m, 6H), 1.44(m, 2H), 1.83(m, 2H), 2.96(dd, 1H), 3.08(dd, 1H), 3.33(t, 2H), 4.25(m, 1H), 5.0(s, 1H), 5.1(d, 1H), 6.8(d, 2H), 7.0(d, 2H), 7.43(m, 5H), 7.73(d, 1H), 7.83(d, 1H), 8.11(s, 1H)

Using (D)-3-(4-(2-phenethyl)oxyphenyl)-2-aminopropionic acid methylester hydrochloride obtained in Example 61, the following titled compound, (2R)-2-[(2-heptylthiobenzthiazol-6-sulfonyl)amino]-3-(4-(2-phenethyl)oxyphenyl)propionic acid, was prepared in a similar manner as aboves.

^{1}H NMR(300MHz, $CDCl_3$): δ 0.9(t, 3H), 1.26(m, 6H), 1.45(m, 2H), 1.83(m, 2H), 2.9(dd, 1H), 3.09(m, 3H), 3.4(m, 2H), 4.09(t, 2H), 4.25(m, 1H), 5.3(d, 1H), 6.7(d, 2H), 7.0(d, 2H), 7.3(m, 5H), 7.85(dd, 2H), 8.12(s, 1H)

Using (D)-3-(4-(3-phenyl-1-propyl)oxyphenyl)-2-aminopropionic acid methylester hydrochloride obtained in Example 62, the following titled compound, (2R)-2-[(2-heptylthiobenzthiazol-6-sulfonyl)amino]-3-(4-(3-phenyl-1-propyl)oxyphenyl)propionic acid, was prepared in a similar manner as aboves.

^{1}H NMR(300MHz, $CDCl_3$): δ 0.85(t, 3H), 1.27(m, 6H), 1.42(m, 2H), 1.78(m, 2H), 2.06(m, 2H), 2.88(dd, 1H), 3.02(dd, 1H), 3.31(t, 2H), 3.83(t, 2H), 4.18(m, 1H), 5.75(d, 1H), 6.64(d, 2H), 6.97(d, 2H), 7.16(m, 5H),

7.79(dd, 2H), 8.06(s, 1H), 8.85(s, 1H)

Using (D)-3-(4-(3-phthalimido-1-propyl)oxyphenyl)-2-aminopropionic acid methylester hydrochloride obtained in Example 63, the following titled compound, (2R)-2-[(2-heptylthiobenzthiazol-6-sulfonyl)amino]-3-(4-(3-phthalimido-1-propyl)oxyphenyl)propionic acid, was prepared in a similar manner as aboves.

^{1}H NMR(300MHz, $CDCl_3$): δ 0.88(t, 3H), 1.23(m, 6H), 1.43(m, 2H), 1.83(m, 2H), 2.15(m, 2H), 2.90(m, 2H), 3.36(t, 2H), 3.93(m, 4H), 4.2(m, 1H), 5.3(d, 1H), 6.62(d, 2H), 6.9(d, 2H), 7.71(m, 3H), 7.84(m, 3H), 8.11(s, 1H)

Using (±)-2-amino-4-phenylbutyric acid methylester hydrochloride synthesized in Example 56, the following titled compound, (±)-2-[(2-heptylthiobenzthiazol-6-sulfonyl)amino]-4-phenylbutyric acid, was prepared in a similar manner as aboves.

^{1}H NMR(300MHz, $CDCl_3$): δ 0.9(t, 3H), 1.30(m, 6H), 1.46(m, 2H), 1.82(p, 2H), 2.0(m, 1H), 2.17(m, 1H), 2.72(m, 2H), 3.32(t, 2H), 4.0(m, 1H), 5.32(d, 1H), 7.0(d, 2H), 7.25(m, 3H), 7.85(dd, 2H), 8.24(s, 1H)

Using (±)-2-amino-5-phenylvaleric acid methylester hydrochloride obtained in Example 57, (±)-2-[(2-heptylthiobenzthiazol-6-sulfonyl)amino]-5-phenylvaleric acid was prepared in a similar manner as aboves.

^{1}H NMR(300MHz, $CDCl_3$): δ 0.89(t, 3H), 1.31(m, 6H), 1.45(m, 2H), 1.67(m, 3H), 1.82(m, 3H), 2.58(m, 2H), 3.32(t, 2H), 4.0(m, 1H), 5.23(d, 1H), 7.0(d, 2H), 7.25(m, 3H),

7.84(dd, 2H), 8.26(s, 1H)

Example 65: (2R)-N-hydroxy-2-[(2-heptylthiobenzthiazol-6-sulfonyl)amino]-3-(4-allyloxy) phenylpropionic amide

(2R)-2-[(2-heptylthiobenzthiazol-6-sulfonyl)amino]-3-(4-allyloxy)phenylpropionic acid(0.17g, 0.31mmol) prepared in Example 64 was dissolved in dichloromethane(2mL) and cooled down to 0℃. Then, oxalylchloride(0.14mL, 5equi.) and DMF of catalytic amount were added. After reaction for 3 hours at RT, the reaction solution was distilled under reduced pressure to remove the solvent and dried under reduced pressure to give (2R)-2-[(2-heptylthiobenzthiazol-6-sulfonyl)amino]-3-(4-allyloxy)phenylpropionyl chloride which was then dissolved in THF(1mL). Hydroxylamine hydrochloride(0.215g, 10equi.) and $NaHCO_3$(0.260g, 10equi.) were dissolved in THF/H_2O(1mL/1mL) and cooled down to 0℃. The acid chloride/THF solution was slowly added to hydroxylamine solution while maintaining the temperature of 0℃. After 1 hour, the solvent was removed from the reaction solution. Then, the product was extracted with ethylacetate(5mL), washed with H_2O and 0.1N HCl, dried over anhydrous $MgSO_4$, distilled under reduced pressure and vacuum-dried to prepare the titled compound, (2R)-N-hydroxy-2-[(2-heptylthiobenzthiazol-6-sulfonyl)amino]-3-(4-allyloxy)phenylpropionic amide (0.157g, 90%).

^1H NMR(300MHz, $CDCl_3$): δ 0.89(t, 3H), 1.3(m, 6H), 1.44(m, 2H), 1.78(m, 2H), 2.74(m, 1H), 3.09(m, 1H), 3.32(t, 1H), 4.09(s, 2H), 5.24(d, 1H), 5.35(d, 1H), 5.93(m, 1H), 6.31(d, 1H), 6.77(m, 4H), 7.6(m, 2H), 7.85(s, 1H), 10.6(s, 1H)

Using (2R)-2-[(2-heptylthiobenzthiazol-6-sulfonyl) amino]-3-(4-propargyloxy)phenylpropionic acid obtained in Example 64, the following titled compound, (2R)-N-hydroxy-2-[(2-heptylthiobenzthiazol-6-sulfonyl)amino]-3-(4-propargyloxy)phenylpropionic amide, was prepared in a similar manner as aboves.

^{1}H NMR(300MHz, $CDCl_3$): δ 0.88(t, 3H), 1.23(m, 6H), 1.43(m, 2H), 1.80(m, 2H), 2.47(d, 1H), 2.8(m, 1H), 3.05(m, 1H), 3.32(t, 2H), 4.03(m, 1H), 4.42(s, 2H), 6.40(d, 2H), 6.50(m, 1H), 6.78(d, 2H), 7.48(d, 1H), 7.62(d, 1H), 7.86(s, 1H), 10.4(s, 1H)

Using (2R)-2-[(2-heptylthiobenzthiazol-6-sulfonyl) amino]-3-(4-benzyloxyphenyl)propionic acid obtained in Example 64, (2R)-N-hydroxy-2-[(2-heptylthiobenzthiazol-6-sulfonyl)amino]-3-(4-benzyloxyphenyl)propionic amide was prepared in a similar manner as aboves.

^{1}H NMR(300MHz, $CDCl_3$): δ 0.87(t, 3H), 1.26(m, 6H), 1.44(m, 2H), 1.83(m, 2H), 2.88(dd, 1H), 3.18(m, 3H), 4.12(m, 1H), 4.75(s, 2H), 6.44(d, 2H), 7.0(d, 2H), 7.3(m, 5H), 7.65(dd, 2H), 7.9(s, 1H)

Using (2R)-2-[(2-heptylthiobenzthiazol-6-sulfonyl) amino]-3-(4-(2-phenylethyl)oxyphenyl)propionic acid obtained in Example 64, (2R)-N-hydroxy-2-[(2-heptylthiobenzthiazol-6-sulfonyl)amino]-3-(4-(2-phenylethyl)oxyphenyl)propionic amide was prepared in a similar manner as aboves.

^{1}H NMR(300MHz, $CDCl_3$): δ 0.88(t, 3H), 1.26(m, 6H), 1.43(m, 2H), 1.81(m, 2H), 2.92(dd, 1H), 3.07(m, 2H), 3.3(m, 1H), 3.37(t, 2H), 3.96(m, 2H) 4.1(m, 1H), 5.2(d, 1H),

6.4(s, 1H), 6.7(d, 2H), 6.93(d, 2H),
7.29(m, 5H), 7.73(d, 1H), 7.81(d, 1H),
7.93(s, 1H), 8.1(s, 1H)

Using (2R)-2-[(2-heptylthiobenzthiazol-6-sulfonyl) amino]-3-(4-(3-phenyl-1-propyl)oxyphenyl) propionic acid obtained in Example 64, (2R)-N-hydroxy-2-[(2-heptylthiobenzthiazol-6-sulfonyl)amino]-3-(4-(3-phenyl-1-propyl)oxyphenyl) propionic amide was prepared in a similar manner as aboves.

^{1}H NMR(300MHz, $CDCl_3$): δ 0.85(t, 3H), 1.23(m, 6H),
1.42(m, 2H), 1.74(m, 2H), 2.01(m, 2H),
2.75(m, 1H), 3.21(m, 3H), 3.74(m, 2H),
4.1(m, 1H), 6.4(d, 2H), 6.8(d, 2H),
7.66(m, 5H), 8.0(m, 3H)

Using (2R)-2-[(2-heptylthiobenzthiazol-6-sulfonyl) amino]-3-(4-(3-phthalimido-1-propyl)oxyphenyl)propionic acid obtained in Example 64, (2R)-N-hydroxy-2-[(2-heptylthiobenzthiazol-6-sulfonyl)amino]-3-(4-(3-phthalimido-1-propyl)oxyphenyl)propionic amide was prepared in a similar manner as aboves.

^{1}H NMR(300MHz, $CDCl_3$): δ 0.88(t, 3H), 1.3(m, 6H),
1.43(m, 2H), 1.77(m, 2H), 2.05(m, 2H),
2.77(m, 3H), 3.0(m, 1H), 3.31(m, 2H),
3.72(t, 2H), 4.05(m, 1H), 6.05(bs, 1H),
6.4(d, 2H), 6.78(d, 2H), 7.21(m, 4H),
7.63(dd, 2H), 7.9(s, 1H), 10.1(bs, 1H)

Using (±)-2-[(2-heptylthiobenzthiazol-6-sulfonyl) amino]-4-phenylbutyric acid obtained in Example 64, (±)-N-hydroxy-2-[(2-heptylthiobenzthiazol-6-sulfonyl)amino]-4-phenylbutyric amide was prepared in a similar manner as aboves.

^{1}H NMR(300MHz, $CDCl_3$): δ 0.88(t, 3H), 1.23(m, 6H), 1.45(m, 2H), 1.77(m, 3H), 2.05(m, 1H), 2.34(m, 2H), 3.33(t, 2H), 3.80(bs, 1H), 6.8(m, 2H), 6.9(m, 3H), 7.8(m, 2H), 8.2(s, 1H), 10.2(bs, 1H)

Using (±)-2-[(2-heptylthiobenzthiazol-6-sulfonyl) amino]-5-phenylvaleric acid obtained in Example 64, (±)-N-hydroxy-2-[(2-heptylthiobenzthiazol-6-sulfonyl)amino] -5-phenylvaleric amide was prepared in a similar manner as aboves.

^{1}H NMR(300MHz, $CDCl_3$): δ 0.88(t, 3H), 1.29(m, 6H), 1.43(m, 2H), 1.70(m, 3H), 1.87(m, 3H), 2.30(m, 2H), 3.36(t, 2H), 3.83(bs, 1H), 6.5(bs, 1H), 6.8(m, 2H), 7.06(m, 3H), 7.82(m, 2H), 8.23(s, 1H), 10.04(bs, 1H)

Example 66: (2R)-2-[(2-chlorobenzthiazol-6-sulfonyl) amino]-3-(4-(3-phthalimido-1-propyl) oxyphenyl)propionic acid methylester

(D)-3-(4-(3-phthalimido-1-propyl)oxyphenyl)-2-aminopropionic acid methylester hydrochloride(0.49g, 1.17mmol) was dispersed in dichloromethane(5mL) and cooled down to 0℃, and triethylamine(0.5mL, 3equi.) was added. 2-Chloro-6-benzthiazolsulfonyl chloride(0.38g, 1.2equi.) prepared in Example 13 was dissolved in dichloromethane(3mL) to give a dichloromethane solution. Then, the dichloromethane solution was added while maintaining the temperature of 0℃. When starting material was exhausted after 1 hour, the organic phase was washed with 1N HCl, dried over anhydrous $MgSO_4$ and distilled under reduced pressure. Then, the product was purified on silica gel chromatography using ethylacetate/n-hexane(1/2) to prepare the titled compound, (2R)-2-[(2-chlorobenzthiazol-6-sulfonyl)amino]

-3-(4-(3-phthalimido-1-propyl)oxyphenyl) propionic acid methylester(0.7g, 97%).

^{1}H NMR(300MHz, $CDCl_3$): δ 2.17(m, 2H), 2.98(m, 2H), 3.52(s, 3H), 3.93(m, 4H), 4.15(m, 1H), 5.4(d, 1H), 6.62(d, 2H), 6.9(d, 2H), 7.73(m, 3H), 7.86(m, 3H), 8.0(s, 1H)

Example 67: (2R)-2-[(2-(4-methoxyphenylthio)benzthiazol-6-sulfonyl)amino]-3-(4-(3-phthalimido-1-propyl)oxyphenyl)propionic acid methylester

(2R)-2-[(2-Chlorobenzthiazol-6-sulfonyl)amino]-3-(4-(3-phthalimido-1-propyl)oxyphenyl)propionic acid methylester(0.24g, 0.39mmol) prepared in a similar manner as in Example 59 was dissolved in MeCN(3mL). K_2CO_3(0.081g, 1.5equi.) were added to the solution in a solid form and then, 4-methoxybenzthiol(0.053mL, 1.1equi.) was added and refluxed for 3 hours. After starting material was exhausted, water/ethylacetate(5mL/10mL) was added and the product was extracted with an organic solvent. The organic phase was washed with NaCl solution, dried over anhydrous $MgSO_4$, distilled under reduced pressure and then, purified on silica gel chromatography using ethylacetate/n-hexane(1/2) to prepare the titled compound, (2R)-2-[(2-(4-methoxyphenylthio)benzthiazol-6-sulfonyl)amino] -3-(4-(3-phthalimido-1-propyl)oxyphenyl)propionic acid methylester(0.2g, 70%).

^{1}H NMR(300MHz, $CDCl_3$): δ 2.13(m, 2H), 2.91(m, 2H), 3.42(s, 3H), 3.85(s, 3H), 3.93(m, 4H), 4.0(m, 1H), 5.27(d, 1H), 6.57(d, 2H), 6.85(d, 2H), 7.0(d, 2H), 7.62(d, 2H), 7.68(m, 3H), 7.81(m, 3H), 8.0(s, 1H)

Example 68: (2R)-2-[(2-(4-methoxyphenylthio)benzthiazol-

6-sulfonyl)amino]-3-(4-(3-phthalimido-1-propyl)oxyphenyl)propionic acid

(2R)-2-[(2-(4-Methoxyphenylthio)benzthiazol-6-sulfonyl)amino]-3-(4-(3-phthalimido-1-propyl)oxyphenyl) propionic acid methylester (0.196g, 0.27mmol) prepared in Example 61 was dissolved in THF/H_2O(2mL/2mL), and LiOH(0.057g, 5equi.) was added and refluxed for 12 hours. Then, the reaction solution was distilled under reduced pressure to remove the solvent and treated with 1N HCl. The product was extracted with ethylacetate(10mL). The separated organic phase was washed with NaCl solution, dried over anhydrous $MgSO_4$, distilled under reduced pressure and dried under vacuum to prepare the titled compound, (2R)-2-[(2-(4-methoxyphenylthio)benzthiazol-6-sulfonyl)amino]-3-(4-(3-phthalimido-1-propyl)oxyphenyl) propionic acid(0.15g, 80%).

^{1}H NMR(300MHz, MeOH-d_4): δ 2.09(m, 2H), 2.6(dd, 1H), 2.9(dd, 1H), 3.87(s, 3H), 3.95(m, 4H), 4.0(m, 1H), 6.25(d, 1H), 6.51(d, 2H), 6.87(d, 2H), 7.12(d, 2H), 7.55(m, 5H), 7.71(m, 3H), 7.95(s, 1H)

Example 69: Preparation of N-hydroxy-(2R)-3-methyl-2-[(2-n-hexylthiobenzthiazol-6-sulfonyl) ethoxycarbonylmethylamino]butyric amide

(2R)-3-Methyl-2-[(2-n-hexylthiobenzthiazol-6-sulfonyl)amino]butanoic acid(7.9 g, 0.018mol) prepared in Example 18-7 was dissolved in acetone(100mL) and the solution was added to diphenyldiazomethane(0.02 mole) acetone solution at RT. The reaction solution was stirred for 12 hours at RT, concentrated and crystallized with n-hexane to give 11.0g(100%) of (2R)-3-methyl-2-[(2-n-hexylthiobenzthiazol-6-sulfonyl)amino] butanoic acid diphenylmethylester. (2R)-3-Methyl-2-[(2-

n-hexylthiobenzthiazol-6-sulfonyl)amino]butanoic acid diphenylmethylester(1.0g, 1.7 mmol) was dissolved in acetone(3mL). K_2CO_3(0.47g, 2.0equi.) and ethylbromoacetate(0.204mL, 1.1equi.) were added to the solution and then, the reaction solution was reacted at 50°C for 12 hours. Then, the reaction solution was distilled under reduced pressure to remove the solvent and the product was extracted with water/ethylacetate. The organic phase was treated with anhydrous $MgSO_4$ to remove the solvent and give (2R)-3-methyl-2-[(2-n-hexylthiobenzthiazol-6-sulfonyl) ethoxycarbonylmethyl amino]butanoic acid diphenylmethylester (1.14g, 100%). Without further purification, the compound was dissolved in CH_2Cl_2(50mL). Then, TFA(1.29mL, 10.0 eq) and anisole(0.55 mL, 3eq) were added and the reaction solution was subjected at RT for 2 hours. Then, the solvent was removed from the solution, which was then treated with n-hexane to give (2R)-3-methyl-2-[(2-n-hexylthiobenzthiazol-6-sulfonyl) ethoxycarbonylmethyl amino]butanoic acid(1.0g). The product was dissolved in dichloromethane(25ml) and the solution was cooled down to 0°C. Oxalylchloride(0.73mL, 5equi.) and DMF of catalytic amount were added, and reacted for 3 hours at RT. Then, the reaction solution was distilled under reduced pressure to remove solvent and dried under reduced pressure to give (2R)-3-methyl-2-[(2-n-hexylthiobenzthiazol-6-sulfonyl) ethoxycarbonylmethyl amino]butanoic acid chloride which was then dissolved in THF(20mL). Hydroxylamine hydrochloride(1.16g, 10equi.) and $NaHCO_3$(2.83g, 12equi.) were dissolved in THF/H_2O(20mL/20mL) and cooled down to 0℃ to prepare hydroxylamine solution. The acid chloride/THF solution thus obtained was slowly added to the hydroxylamine solution. After 1 hour, the solvent was removed from the reaction solution. The product was extracted with ethylacetate(50mL) and then, washed with H_2O and 0.1N HCl and dried over $MgSO_4$ to prepare 1.23g of N-hydroxy-(2R)-

3-methyl-2-[(2-n-hexylthiobenzthiazol-6-sulfonyl)ethoxycarbonyl methylamino]butyric amide.

^{1}H NMR(300MHz, MeOH-d_4): δ 0.84(d, 3H), 0.93(d, 3H), 1.37(m, 6H), 1.52(m, 6H), 1.86(m, 2H), 2.1(m, 1H), 3.3(t, 2H), 4.3(m, 5H), 2.09(m, 2H), 2.6(dd, 1H), 2.9(dd, 1H), 3.87(s, 3H), 6.65(bs, 1H), 7.97(m, 2H), 8.37(m, 1H), 9.33(bs, 1H)

Example 70: *In vitro* inhibition on gelatinase A(MMP-2)

The present test was accomplished by measuring the fluorescence intensity of a fluorescent material(7-methoxycoumarin-4-acetyl-Pro-Leu-Gly) produced from the cleavage of a fluorescent synthetic peptide substrate((7-methoxycoumarin-4-acetyl-Pro-Leu-Gly-Leu-β-(2,4-dinitrophenylamino)Ala-Ala-Arg-NH_2(Sigma Chem. Co., U.S.A.)) by gelatinase A(Boehringer Manneheim cat# 1782916, from human fibrosarcoma cells).

Enzymatic reaction employing a fluorescent synthetic substrate was accomplished by putting test compounds, TNBC buffer solution(25mM Tris-HCl, pH 7.5, 0.1M NaCl, 0.01% Brij-35, 5mM $CaCl_2$), gelatinase A(final concentration in well: 4.17nM) activated with 1 mM of APMA(aminophenylmercuric acetate) for 30 minutes at 37°C just before the enzymatic reaction and the substrate, fluorescent synthetic peptide(final concentration in well: 9.15uM) in 96 well plate and then reacting for 30 minutes at 37°C, and the fluorescence intensity was measured at excitation 328nm and emission 393nm by spectrofluorimeter(Fmax(molecular device)). The inhibition rate(%) was calculated from the following equation:

$$\text{Inhibition Rate}(\%) = \frac{(D\text{-}C)\text{-}(B\text{-}A)}{(D\text{-}C)} X100$$

wherein,

A represents fluorescence intensity before the reaction with an inhibitor;

B represents fluorescence intensity after the reaction with an inhibitor;

C represents fluorescence intensity before the reaction without an inhibitor; and,

D represents fluorescence intensity after the reaction without an inhibitor.

Example 71: *In vitro* inhibition on gelatinase B(MMP-9)

In vitro inhibition rate on gelatinase B(MMP-9) was measured in a similar manner as in Example 70, except for employing gelatinase B(Boehringer Manneheim cat# 1758896, from human blood) and the concentration of gelatinase B(final concentration in well: 2.715nM) and the concentration of the substrate, fluorescent synthetic peptide(final concentration in well: 4.575uM).

Example 72: *In vitro* inhibition on collagenase(MMP-1)

In vitro inhibition rate on collagenase(MMP-1) was measured in a similar manner as in Example 70, except for employing collagenase(AngioLab. Co., Ltd) and the concentration of the collagenase(final concentration in well: 7.25nM).

Table 1

Number	R_1	R_2	R_4	R_3	IC_{50} (nM) MMP-2	IC_{50} (nM) MMP-9	IC_{50} (nM) MMP-1
1	n-C_5H_{11}	CH_3	H	CO_2H	38.9	180.0	
2	n-C_5H_{11}	CH_3	H	CONHOH	0.3	1.0	1600
3	n-C_6H_{13}	CH_3	H	CO_2H	100.0	1520.0	
4	n-C_6H_{13}	CH_3	H	CONHOH	0.5	3.0	
5	n-C_5H_{11}	CH_3	Bn	CO_2H	63.5	130.0	
6	n-C_5H_{11}	CH_3	Bn	CONHOH	1.4	1.0	
7	c-Hexyl-CH_2	CH_3	H	CO_2H	14.7	190.0	
8	c-Hexyl-CH_2	CH_3	H	CONHOH	0.5	3.0	
9	c-Hexyl-CH_2	CH_3	Bn	CO_2H	23.6	110.0	
10	c-Hexyl-CH_2	CH_3	Bn	CONHOH	1.2	2.0	
11	n-C_5H_{11}	$PhCH_2$	H	CONHOH	0.4	1.5	13896
12	n-C_5H_{11}	$PhCH_2$	Bn	CONHOH	2.3	2.6	
13	n-C6H_{13}	$PhCH_2$	H	CONHOH	1.2	8.0	25640
14	c-Hexyl-CH_2	$PhCH_2$	H	CONHOH	1.2	9.0	
15	c-Hexyl-CH_2	$PhCH_2$	Bn	CONHOH	9.1	22.0	
16	n-C_5H_{11}	$CH_3SCH_2CH_2$	H	CONHOH	0.3	0.6	3013
17	n-C_6H_{13}	$CH_3SCH_2CH_2$	H	CONHOH	0.8	3.0	
18	n-C_5H_{11}	$CH_3SCH_2CH_2$	Bn	CONHOH	4.3	3.8	
19	c-Hexyl-CH_2	$CH_3SCH_2CH_2$	H	CONHOH	0.6	3.0	
20	n-C_5H_{11}	$HO_2CCH_2CH_2$	H	CO_2H	47.0	610.0	
21	n-C_6H_{13}	$HO_2CCH_2CH_2$	H	CO_2H	76.2	800.0	330400
22	n-C_6H_{13}	HO_2CCH_2	H	CO_2H	95.0	420.0	311430
23	n-C_5H_{11}	Iso-Butyl	H	CONHOH	0.2	0.4	3380
24	n-C_6H_{13}	Iso-Butyl	H	CONHOH	0.4	2.0	7070
25	n-C_5H_{11}	2-IndoleCH_2	H	CO_2H	6.4	20.0	11909
26	n-C_6H_{13}	2-IndoleCH_2	H	CO_2H	9.1	20.0	
27	n-C_5H_{11}	2-IndoleCH_2	H	CONHOH	1.5	2.7	
28	n-C_6H_{13}	2-IndoleCH_2	H	CONHOH	3.0	6.0	
29	CH_3	Iso-Propyl	H	CO_2H	640.0	4800.0	
30	CH_3	Iso-Propyl	H	CONHOH	5.0	34.0	

31	C_2H_5	Iso-Propyl	H	CO_2H	210.0	7400.0	
32	C_2H_5	Iso-Propyl	H	CONHOH	1.3	16.0	
33	C_2H_5	Iso-Propyl	Bn	CO_2H	1200.0	6280.0	
34	C_2H_5	Iso-Propyl	Bn	CONHOH	6.0	20.4	
35	n-C_3H_7	Iso-Propyl	H	CO_2H	150.0	4100.0	
36	n-C_3H_7	Iso-Propyl	H	CONHOH	0.2	4.0	
37	n-C_3H_7	Iso-Propyl	Bn	CO_2H	900.0	3180.0	
38	n-C_3H_7	Iso-Propyl	Bn	CONHOH	2.5	5.0	
39	n-C_4H_9	Iso-Propyl	H	CO_2H	1.6	144.0	3819
40	n-C_4H_9	Iso-Propyl	H	CONHOH	0.3	0.2	
41	n-C_4H_9	Iso-Propyl	Bn	CO_2H	270.0	700.0	
42	n-C_4H_9	Iso-Propyl	Bn	CONHOH	2.7	3.0	
43	n-C_5H_{11}	Iso-Propyl	H	CO_2H	16.0	189.0	
44	n-C_5H_{11}	Iso-Propyl	H	CONHOH	0.2	0.5	2606
45	n-C_5H_{11}	Iso-Propyl	Bn	CO_2H	400.0	660.0	
46	n-C_5H_{11}	Iso-Propyl	Bn	CONHOH	3.8	3.5	
47	n-C_6H_{13}	Iso-Propyl	H	CO_2H	15.0	178.0	172380
48	n-C_6H_{13}	Iso-Propyl	H	CONHOH	0.6	3.1	2780
49	n-C_6H_{13}	Iso-Propyl	Bn	CO_2H	385.0	1767.0	
50	n-C_6H_{13}	Iso-Propyl	Bn	CONHOH	3.0	4.9	

51	n-C_7H_{15}	Iso-Propyl	H	CO_2H	5.0	496.0	12504
52	n-C_7H_{15}	Iso-Propyl	H	CONHOH	0.3	2.0	6303
53	n-C_7H_{15}	Iso-Propyl	Bn	CO_2H			
54	n-C_7H_{15}	Iso-Propyl	Bn	CONHOH			
55	n-C_8H_{17}	Iso-Propyl	H	CO_2H	9.0	764.0	
56	n-C_8H_{17}	Iso-Propyl	H	CONHOH	0.5	3.0	
57	n-C_8H_{17}	Iso-Propyl	Bn	CO_2H	780.0	5210.0	
58	n-C_8H_{17}	Iso-Propyl	Bn	CONHOH	28.0	77.0	
59	n-$C_{12}H_{25}$	Iso-Propyl	H	CO_2H	170.0	4210.0	
60	n-$C_{12}H_{25}$	Iso-Propyl	H	CONHOH	17.0	77.0	
61	n-$C_{12}H_{25}$	Iso-Propyl	Bn	CO_2H	23400.0	59600.0	
62	n-$C_{12}H_{25}$	Iso-Propyl	Bn	CONHOH	0.7	27.0	
63	c-HexylCH_2	Iso-Propyl	H	CO_2H	9.3	202.0	
64	c-HexylCH_2	Iso-Propyl	H	CONHOH	0.046	0.24	4671
65	c-Hexyl$CH_2CH_2CH_2$	Iso-Propyl	H	CO_2H	8.0	0.7	
66	c-Hexyl$CH_2CH_2CH_2$	Iso-Propyl	H	CONHOH	0.7	5.8	
67	c-Pentyl	Iso-Propyl	H	CO_2H	690.0	8250.0	
68	c-Pentyl	Iso-Propyl	H	CONHOH	1.4	5.0	
69	PhCH_2	Iso-Propyl	H	CO_2H	90.0	99.0	
70	PhCH_2	Iso-Propyl	H	CONHOH	0.7	0.7	

71	p-ClPhCH_2	Iso-Propyl	H	CO_2H	40.0	79.0	
72	p-ClPhCH_2	Iso-Propyl	H	CONHOH	0.2	0.6	2331
73	p-MeOPhCH_2	Iso-Propyl	H	CO_2H	36.0	420.0	
74	p-MeOPhCH_2	Iso-Propyl	H	CONHOH	0.8	0.2	
75	Ph$CH_2CH_2CH_2$	Iso-Propyl	H	CO_2H	1120.0	3190.0	
76	Ph$CH_2CH_2CH_2$	Iso-Propyl	H	CONHOH	10.7	34.0	
77	Ph	Iso-Propyl	H	CO_2H	410.0	1880.0	
78	Ph	Iso-Propyl	H	CONHOH	0.6	2.3	
79	p-Me-Ph	Iso-Propyl	H	CO_2H	250.0	1710.0	
80	p-Me-Ph	Iso-Propyl	H	CONHOH	0.74	2.0	
81	p-Br-Ph	Iso-Propyl	H	CO_2H	320.0	930.0	
82	p-Br-Ph	Iso-Propyl	H	CONHOH	5.3	28.0	
83	p-F-Ph	Iso-Propyl	H	CO_2H	1430.0	451.0	
84	p-F-Ph	Iso-Propyl	H	CONHOH	8.7	23.0	
85	p-MeO-Ph	Iso-Propyl	H	CO_2H	290.0	740.0	
86	p-MeO-Ph	Iso-Propyl	H	CONHOH	0.2	0.2	13432
87	p-n-Bu-Ph	Iso-Propyl	H	CO_2H	120.0	660.0	
88	p-n-Bu-Ph	Iso-Propyl	H	CONHOH	0.6	2.0	
89	n-C_4H_9	$PhCH_2$	H	PO_3H_2	52200.0	4491610	
90	n-C_6H_{13}	$PhCH_2$	H	PO_3H_2	40140.0	289770	
91	c-HexylCH_2	$PhCH_2$	H	PO_3H_2	20560.0	537500	

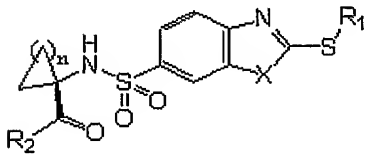


Table 2

Number	R_1	R_2	X	N	IC_{50}(nM) MMP-2	IC_{50}(nM) MMP-9
1	n-C_4H_9	OH	S	1	1219	7535
2	n-C_4H_9	NHOH	S	1	18.4	26.6
3	n-C_4H_9	OH	S	3	651	3922
4	n-C_4H_9	NHOH	S	3	7.0	20.0
5	n-C_4H_9	OH	S	4	246	1364
6	n-C_4H_9	NHOH	S	4	5.9	14.2

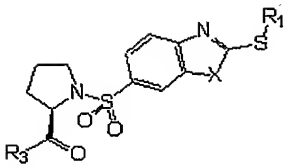


Table 3

Number	R_1	R_3	X	IC_{50} (nM) MMP-2	IC_{50} (nM) MMP-9
1	$n-C_5H_{11}$	OH	S	1210	8050
2	$n-C_5H_{11}$	NHOH	S	5.8	4.2
3	$n-C_6H_{13}$	OH	S	944	14100
4	$n-C_6H_{13}$	NHOH	S	5.6	1

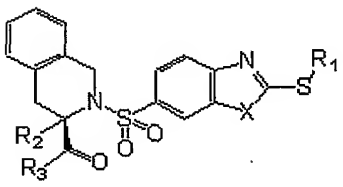


Table 4

Number	R_1	R_2	R_3	X	IC_{50} (nM) MMP-2	IC_{50} (nM) MMP-9
1	$n-C_5H_{11}$	H	OH	S	380	1290
2	$n-C_5H_{11}$	H	NHOH	S	0.4	0.6
3	$n-C_5H_{11}$	CH3	OH	S	37460	207257
4	$n-C_5H_{11}$	CH3	NHOH	S	1000	2052

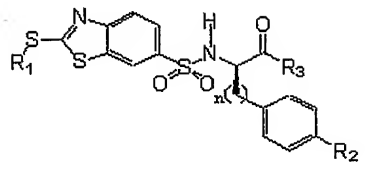


Table 5

Number		R_1	R_2	R_3	N	IC_{50} (nM) MMP-2	IC_{50} (nM) MMP-9	IC_{50} (μ M) MMP-1
1	(±)	n-C_7H_{15}	H	OH	2	119	1550	
2	(±)	n-C_7H_{15}	H	NHOH	2	3.4	39	
3	(±)	n-C_7H_{15}	H	OH	3	69	742	
4	(±)	n-C_7H_{15}	H	NHOH	3	1.63	6	
5	(±)	n-C_7H_{15}	$HCCCH_2$-O-	OH	1	81	84	
6	(±)	n-C_7H_{15}	$HCCCH_2$-O-	NHOH	1	3.63	2.74	
7	(R)	n-C_7H_{15}	$HCCCH_2$-O-	OH	1	56	3072	
8	(R)	n-C_7H_{15}	$HCCCH_2$-O-	NHOH	1	1.6	9.8	
9	(R)	n-C_7H_{15}	$HCCHCH_2$-O-	OH	1	137	7915	
10	(R)	n-C_7H_{15}	$HCCHCH_2$-O-	NHOH	1	1.2	8	
11	(R)	n-C_7H_{15}	$PhCH_2CH_2CH_2$-O-	OH	1	704	28770	

12	(R)	n-C_7H_{15}	$PhCH_2$-O-	NHOH	1	6	87	
13	(R)	n-C_7H_{15}	$PhCH_2$-O-	OH	1	684	1430	
14	(R)	n-C_7H_{15}	$PhCH_2CH_2$-O-	NHOH	1	23	134	
15	(R)	n-C_7H_{15}	$PhCH_2CH_2$-O-	OH	1	508	2330	
16	(R)	n-C_7H_{15}	$PhCH_2CH_2CH_2$-O-	NHOH	1	2	22	
17	(R)	n-C_7H_{15}	Phthalimino-$(CH_2)_3$-O-	OH	1	40	476	
18	(R)	n-C_7H_{15}	Phthalimino-$(CH_2)_3$-O-	NHOH	1	0.8	8	
19	(R)	n-C_5H_{11}	$PhCH_2CH_2CH_2$-O-	OH	1	340	915	
20	(R)	n-C_5H_{11}	$PhCH_2CH_2CH_2$-O-	NHOH	1	4.9	9.1	
21	(R)	n-C_5H_{11}	Phthalimino-$(CH_2)_3$-O-	OH	1	40	129	
22	(R)	n-C_5H_{11}	Phthalimino-$(CH_2)_3$-O-	NHOH	1	0.9	1.9	
23	(R)	n-C_6H_{13}	$HCCHCH_2$-O-	OH	1	101	536	1144.4
24	(R)	n-C_6H_{13}	$HCCHCH_2$-O-	NHOH	1	1.5	5	27.6
25	(R)	n-C_6H_{13}	$HCCCH_2$-O-	OH	1	62	462	
26	(R)	n-C_6H_{13}	$HCCCH_2$-O	NHOH	1	6.4	9	45.8
27	(R)	n-C_6H_{13}	$PhCH_2CH_2CH_2$-O-	OH	1	251	1495	
28	(R)	n-C_6H_{13}	$PhCH_2CH_2CH_2$-O-	NHOH	1	7.6	30	139.7
29	(R)	n-C_6H_{13}	Phthalimino-$(CH_2)_3$-O-	OH		40	223	
30	(R)	n-C_6H_{13}	Phthalimino-$(CH_2)_3$-O-	NHOH		1.6	1.1	10.2
31	(R)	p-C_1PhCH_2	Phthalimino-$(CH_2)_3$-O-	OH		193	332	
32	(R)	p-C_1PhCH_2	Phthalimino-$(CH_2)_3$-O-	NHOH		4.5	5.8	
33	(R)	p-MeO-Ph	Phthalimino-$(CH_2)_3$-O-	OH		1057	5148	
34	(R)	p-MeO-Ph	Phthalimino-$(CH_2)_3$-O-	NHOH		3.2	7	
35	(R)	c-Pentyl	Phthalimino-$(CH_2)_3$-O-	OH		1144	7956	
36	(R)	c-Pentyl	Phthalimino-$(CH_2)_3$-O-	NHOH		4.7	23.5	

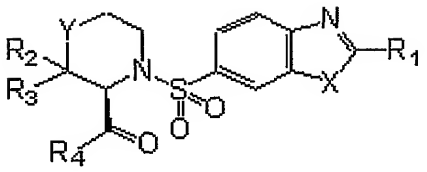
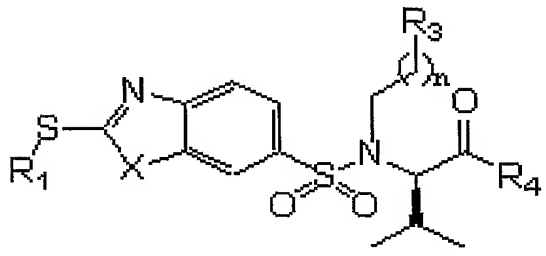


Table 6

Number	R_1	R_2:R_3	R_4	Y	IC_{50}(nM) MMP-2	IC_{50}(nM) MMP-9	IC_{50}(nM) MMP-1
1	n-C_4H_9-S-	CH_3:CH_3	OH	S	483	1474	
2	n-C_4H_9-S-	CH_3:CH_3	NHOH	S	0.4	0.4	
3	n-C_6H_{13}-S-	CH_3:CH_3	OH	S	172	795	
4	n-C_6H_{13}-S-	CH_3:CH_3	NHOH	S	0.3	0.4	150
5	c-HexylCH_2-S-	CH_3:CH_3	OH	S	46	232	
6	c-HexylCH_2-S-	CH_3:CH_3	NHOH	S	0.7	1	
7	MeO-	H:H	OH	CH_2	16100	13400	
8	C_2H_5-S-	H:H	OH	CH_2	1560	3030	
9	C_2H_5-S-	H:H	NHOH	CH_2	2.0	9.0	
10	n-C_4H_9-S-	H:H	OH	CH_2	120	1820	
11	n-C_4H_9-S-	H:H	NHOH	CH_2	1.3	0.7	
12	n-C_6H_{13}-S-	H:H	OH	CH_2	86	2270	
13	n-C_6H_{13}-S-	H:H	NHOH	CH_2	1.8	2.8	
14	n-C_7H_{15}-S-	H:H	OH	CH_2	49	2250	
15	n-C_7H_{15}-S-	H:H	NHOH	CH_2	1.7	8.9	
16	n-C_8H_{17}-S-	H:H	OH	CH_2	53	1950	
17	n-C_8H_{17}-S-	H:H	NHOH	CH_2	3.6	21.8	
18	c-HexylCH_2-S-	H:H	OH	CH_2	31	680	
19	c-HexylCH_2-S-	H:H	NHOH	CH_2	0.5	1.9	



5

Table 7

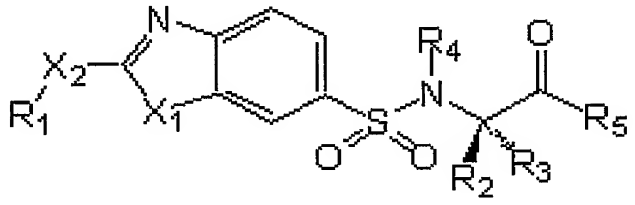
Number	R_1	X	R_3	n	R_4	IC_{50} (nM) MMP-2	IC_{50} (nM) MMP-9
1	Methyl	S	N-Morpholino	1	NHOH	8.8	17.2
2	Methyl	S	N-Morpholino	1	OH	1846	9790
3	n-Hexyl	O	$-CO_2Et$	2	NHOH	19.1	1.5
4	n-Hexyl	O	$-CO_2Et$	2	OH	1800	1118
5	n-Hexyl	O	N-Morpholino	1	NHOH	14.0	4.4
6	n-Hexyl	O	3-Pyridyl	0	NHOH	6.3	1.9
7	c-Hexylmethyl	S	Hydroxyimino-	1	OH	16.2	83.5
8	n-Hexyl	O	Phenyl	0	NHOH		11.4
9	Methyl	S	OH	2	NHOH	7.4	13.1
10	Methyl	S	AcO-	2	NHOH	4.8	6.7
11	c-Hexylmethyl	S	1,3-dioxlane-2-	1	OH	19.9	93.0
12	n-Propyl	S	AcO-	2	NHOH	1.6	2.0
13	n-Propyl	S	OH	2	NHOH	1.5	2.2
14	n-Hexyl	S	AcO-	2	NHOH	0.9	0.7
15	n-Hexyl	S	OH	2	NHOH	0.4	0.4
16	c-Hexylmethyl	S	Phthalimido-1-	2	NHOH	7.4	11.6
17	c-Hexylmethyl	S	Succinimido-1-	2	NHOH	1.8	2.7
18	n-Propyl	S	$-CO_2H$	2	NHOH	2.0	2.2
19	n-Propyl	S	$-CO_2Et$	2	NHOH	1.4	1.7
20	Methyl	S	$-CO_2H$	2	NHOH	6.7	9.3
21	Methyl	S	$-CO_2Et$	2	NHOH	2.7	3.3
22	c-Hexylmethyl	S	$-CO_2H$	3	NHOH	0.9	1.3
23	c-Hexylmethyl	S	$-CO_2Et$	3	NHOH	3.2	3.8
24	c-Hexylmethyl	S	OH	2	NHOH	0.6	1.0
25	c-Hexylmethyl	S	AcO-	2	NHOH	1.6	2.2
26	n-Hexyl	S	$4-CO_2H-Ph-$	0	NHOH	0.5	0.2
27	n-Hexyl	S	$-CO_2H$	4	NHOH	0.2	0.2
28	n-Hexyl	S	$4-MeCO_2-Ph-$	0	NHOH	20.0	15.3
29	n-Hexyl	S	$-CO_2Et$	4	NHOH	4.4	1.2
30	c-Hexylmethyl	S	N-Morpholino	1	NHOH	1.2	1.8
31	c-Hexylmethyl	S	3-Pyridyl	1	NHOH	2.0	2.7
32	c-Hexylmethyl	S	$-CO_2Et$	0	NHOH	4.2	15.1
33	n-Hexyl	S	N-Morpholino	1	NHOH	0.7	0.4
34	n-Hexyl	S	3-Pyridyl	0	NHOH	1.3	0.9
35	n-Hexyl	S	$-CO_2-t-Bu$	0	NHOH	3.2	1.6
36	n-Hexyl	S	$-CO_2Et$	2	NHOH	1.3	0.5
37	n-Hexyl	S	$-CO_2Et$	0	NHOH	2.1	1.5
38	n-Hexyl	S	$-CO_2H$	2	NHOH	0.4	0.2

As clearly illustrated and demonstrated as aboves, the present invention provides novel sulfonamide derivatives, which inhibit MMP activity, their isomers and the pharmaceutically acceptable salts thereof, and a process for preparing the compounds. Since the sulfonamide derivatives of the present invention selectively inhibit MMP activity *in vitro*, the MMP inhibitors comprising the sulfonamide derivatives as an active ingredient can be practically applied for the prevention and treatment of diseases caused by overexpression and overactivation of MMP.

Although the preferred embodiments of the present invention have been disclosed for illustrative purpose, those who are skilled in the art will appreciate that various modifications, additions and substitutions are possible, without departing from the scope and spirit of the invention as described in the accompanying claims.

WHAT IS CLAIMED IS:

1. A compound represented as the following general formula(I), and its isomers and pharmaceutically acceptable salts thereof:



(I)

wherein,

R_1 denotes hydrogen, C_{1-12} alkyl, carbocyclic aryl-lower alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl- lower alkyl, (oxo, amino or thio) C_{3-7} cycloalkyl, (oxo, amino or thio) C_{3-7} cycloalkyl-lower alkyl, C_{2-12} lower alkenyl, C_{2-12} lower alkynyl, carbocyclic aryl, heterocyclic aryl, heterocyclic aryl-lower alkyl, biaryl, halo lower alkyl, biaryl-lower alkylarylalkyl, hydroxy-lower alkyl, alkoxyalkyl, acyloxy-lower alkyl, alkyl or aryl (thio, sulfinyl or sulfonyl) lower alkyl, (amino, mono or dialkylamino) lower alkyl, acylamino lower alkyl, (N-lower alkyl-piperazino, or N-carbocyclic or heterocyclic aryl-lower alkyl piperazino)-lower alkyl or (morpholino, thiomorpholino, piperidino, pyrrolidino or piperidyl)-lower alkyl;

R_2 denotes hydrogen, lower alkyl, carbocyclic aryl-lower alkyl, C_{1-4} carbocyclic aryl-lower alkyl, C_{1-4} heterocyclic aryl-lower alkyl, C_{1-5} alkoxyphenyl-lower alkyl, C_{1-5} alkenoxyphenyl-lower alkyl, C_{1-5} alkynoxyphenyl-lower alkyl, heterocyclic aryl-lower alkyl, hydroxy-lower alkyl, alkoxyalkyl, acyloxy-lower alkyl, thio-lower alkyl, alkyl or aryl-(thio, sulfinyl or sulfonyl) lower alkyl, (amino, mono or dialkylamino) lower alkyl, carboxyl-lower alkyl, (amino, mono or dialkylamino) lower alkyl or acylamino lower alkyl;

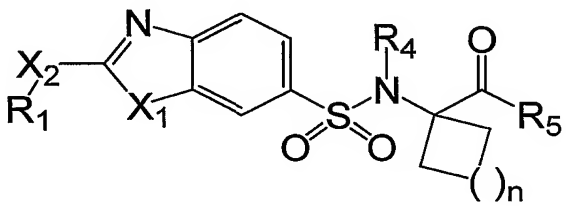
R_3 denotes hydrogen or C_{1-6}-lower alkyl;

R_4 denotes hydrogen, C_{1-12} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-lower alkyl, (oxo, amino or thio) C_{3-7} cycloalkyl, (oxo, amino or thio) C_{3-7} cycloalkyl-lower alkyl, carbocyclic aryl, carbocyclic aryl-lower alkyl, heterocyclic aryl, heterocyclic aryl-lower alkyl, biaryl, biaryl-lower alkyl, halo lower alkyl, hydroxy-lower alkyl, alkoxyalkyl, acyloxy-lower alkyl, alkyl or aryl-(thio, sulfinyl or sulfonyl) lower alkyl, (amino, mono or dialkylamino) lower alkyl, acylamino lower alkyl, carboxyl lower alkyl, (N-lower alkyl-piperazino, or N-carbocyclic or heterocyclic aryl piperazino)-lower alkyl or (morpholino, thiomorpholino, piperidino, pyrrolidino or piperidyl)-lower alkyl;

R_5 denotes hydroxy, alkoxy, halogen, thiol, thioalkoxy or hydroxylamine; and,

X_1 and X_2 denote N-R_7(wherein, R_7 is hydrogen, C_{1-6}-lower alkyl, aryl, heteroaryl or arylalkyl), S or O.

2. The compound of claim 1, wherein linkage of R_2 and R_3 form C_{3-6} carbocyclic or heterocyclic ring represented as the following general formula(I-1):



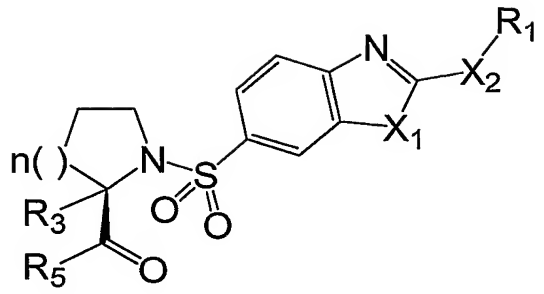
(I-1)

wherein,

R_1, R_4, R_5, X_1 and X_2 are the same as defined in the general formula(I) above; and,

n is an integer of 0 to 4.

3. The compound of claim 1, wherein linkage of R_2 and R_4 form C_{3-7} carbocyclic or heterocyclic ring represented as the following general formula(I-2):



(I-2)

wherein,

R_1, R_3, R_4, R_5, X_1 and X_2 are the same as defined in the general formula(I) above; and,

n is an integer of 0 to 4.

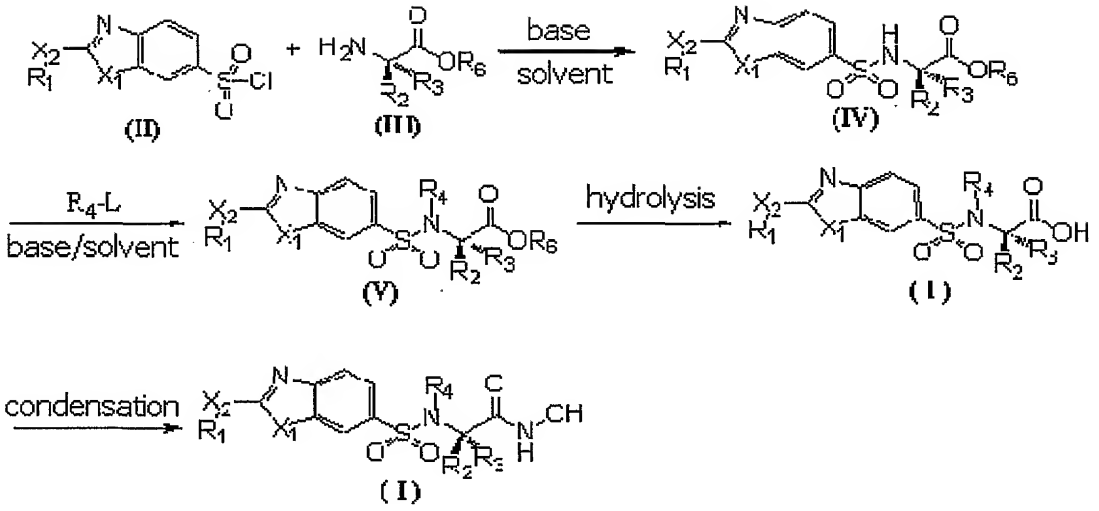
4. The compound of one of claims 1 to 3, wherein the compound inhibits matrix metalloproteinase.

5. A process for preparing a compound represented as the general formula(I), which comprises:

(i) reacting sulfonyl halide(II) with compound(III) in an organic solvent in the presence of a base to give an intermediate compound(IV);

(ii) reacting the intermediate compound(IV) with R_4-L(L: reactive leaving group) in an organic solvent in the presence of a base to give an intermediate compound(V); and,

(iii) hydrolyzing the intermediate compound(V) into a compound(I, R_5:OH), or further condensing the compound(I, R_5:OH) to prepare a compound(I, R_5:NHOH).



wherein,

R_1, R_2, R_3, R_4, X_1 and X_2 are the same as defined in the general formula(I) above; and,

R_6 is a substituent used as a protecting group of amino acid.

6. The process for preparing a compound represented as the general formula(I) of claim 5, wherein the hydrolysis in step(iii) is performed in the presence of a base, lithiumhydroxide.

7. A process for preparing a compound represented as the general formula(I), which comprises:

(i) chlorosulfonylating a compound(VI) to give a compound(VII);

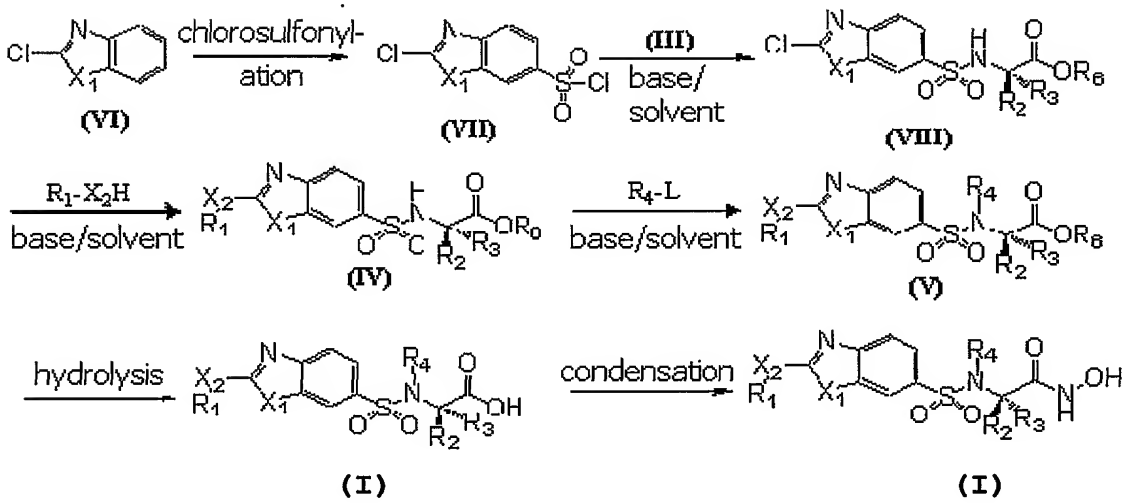
(ii) reacting the compound(VII) with amino acid derivative(III) in an organic solvent in the presence of base to give an intermediate compound(VIII);

(iii) heating the intermediate compound(VIII)

and R_1-X_2H together at 70 to 80°C in an organic solvent in the presence of base to give an intermediate compound(IV);

(iv) reacting the intermediate compound(IV) with R_4-L(L: reactive leaving group) in an organic solvent in the presence of base to give an intermediate compound(V); and,

(v) hydrolyzing the intermediate compound(V) into a compound(I, R_5:OH), or further condensing the compound(I, R_5:OH) to prepare a compound(I, R_5:NHOH).



wherein,

R_1, R_2, R_3, R_4, X_1 and X_2 are the same as defined as in the general formula(I) above; and,

R_6 is a substituent used as a protecting group of amino acid.

8. The process for preparing a compound represented as the general formula(I) of claim 7, wherein the hydrolysis in step(v) is performed in the presence of a base, lithiumhydroxide.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR01/00585

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07D 277/68, C07D 263/58, A61K 31/423

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimun documentation searched (classification system followed by classification symbols)

IPC7: C07D; A61K

Documentation searched other than minimun documentation to the extent that such documents are included in the fileds searched

Electronic data base consulted during the internationl search (name of data base and, where practicable, search trerms used)

CASLINK; ESPACENET

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98/03166 A (MONSANTO CO.), 29. Jan. 1998, see the whole document	1-8
A	WO 98/07742 A (ZENECA LTD.), 26. Feb. 1998, see the whole document	1-8
A	WO 98/09934 A (WARNER LAMBERT CO.), 12. Mar. 1998, see the whole document	1-8
A	WO 99/41246 A (DU PONT PHARM. CO.), 19. Aug. 1999, see the whole document, (Family; none)	1-8
A	WO 99/52862 A (PFIZER PROD. INC.), 21. Oct. 1999, see the whole document	1-8

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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"X" document of particular relevence; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
23 JULY 2001 (23.07.2001)	25 JULY 2001 (25.07.2001)

Name and mailing address of the ISA/KR	Authorized officer
Korean Intellectual Property Office Government Complex-Daejeon, Dunsan-dong, Seo-gu, Daejeon Metropolitan City 302-701, Republic of Korea	LEE, Yu Hyung
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR01/00585

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 98/03166 A	29. 01. 98	NO 990247 A NO 990247 AO	19. 03. 99 20. 01. 99
WO 98/07742 A	26. 02. 98	AP 9701079 AO GB 9715962 AO	31. 10. 97 01. 10. 97
WO 98/09934 A	12. 03. 98	CA 2256716 AA	12. 03. 98
WO 99/52862 A	21. 10. 99	HU 9901043 AO	28. 06. 99